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WARNING: *"Suddenly, the heart rate and her nervousness increased, and it was discovered that she had purchased huge quantities of thyroid while unobserved." (Goldfinger, D.: Ann. Int. Med. 24:701 (April) 1946.)*

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PROLOID

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CLINICAL METHOD FOR THE CHROMATOGRAPHIC-COLORIMETRIC DETERMINATION OF URINARY 17-KETOSTEROIDS. I.

ELISABETH DINGEMANSE, LEONORA G. HUIS IN'T VELD AND B. M. DE LAAT

From the Pharmaco-Therapeutic Laboratory of the University of Amsterdam, Holland

DURING recent years determinations of the 17-ketosteroid content of urine have been made in addition to or instead of the biological assay of androgens. The results obtained are believed to reflect the activity of both the gonads and the adrenals. The 17-ketosteroid determination is performed colorimetrically according to the method of Zimmermann (21). In this assay m-dinitrobenzene is used, which yields a wine red color with 17-ketosteroids in an alkaline medium. Since urinary extracts are usually very dark in color, which prevents a colorimetric assay, several investigators interpose a chromatographic analysis. For this purpose the extract, which in most cases has undergone some preliminary chemical purification, is dissolved in carbon tetrachloride, benzene or ethanol. This solution is passed through a column of Al_2O_3, standardized according to Brockmann. The column is rinsed and eluated. The eluate is withdrawn in one or several fractions in which the 17-ketosteroids can be determined. Usually this assay is performed with the total eluate. If ethanol is used for the elution the 17-ketosteroids are washed out very quickly and little time is required for the procedure. The disadvantage of this method is that only quantitative differences of the total 17-ketosteroids are measured, while qualitative differences of the 17-ketosteroids excreted by normal persons and those suffering from various disorders are likely to be significant.

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The experiments reported here were made with a view to determining whether such qualitative differences can be demonstrated in certain pathol logic cases and an attempt has been made to adapt the method for clinica use. If this method makes it possible to determine the different 17-keto steroids including dehydro-iso-androsterone and androsterone quantita tively in the same specimen, the cumbersome and expensive biological assay for which very few clinics are equipped, can be abandoned. The bio logical activity of trans-dehydroandrosterone and of androsterone can also be calculated from their chemical assay.

A. Preparation of the urinary extracts

The urine is extracted according to the method described by Dingemanse and Laqueur (8). The urine of normal persons is hydrolyzed with 80 cc. of 25 per cent hydrochloric acid per liter. Pathological urine is extracted prior to the hydrolyzing three times for five hours each time with benzene on the boiling waterbath. Subsequently the extracted urine is treated as described for normal urines. The acid and neutral extracts are united for the chromatographic analysis.

B. Chromatographic colorimetric assay

Usually half a liter of urine from normal persons is used. A still smaller volume suffices in cases of adrenal cortical hyperplasia, in which large quantities of 17-ketosteroids occur. The extract is evaporated to dryness and the residue is dissolved in 50 cc. of benzene. This solution is passed through a column (diameter, 15 mm.; height, 10 cm.) of Al_2O_3 standardized according to Brockmann. Thereupon, 50 cc. of each of the following solvents are passed through the column and each fraction is collected separately:

7×50 cc. benzene
24×50 cc. benzene containing 0.1 per cent ethanol
10×50 cc. benzene containing 0.5 per cent ethanol
2×50 cc. ethanol

The 17-ketosteroid content of each fraction is determined separately with the color reaction of Zimmermann as modified by Callow *et al.* (6). One tenth of the volume of the eluate is used for the colorimetric assay against a 1 mg. per cent solution of dehydro-iso-androsterone and the microgram values obtained are plotted as the ordinate against an abscissa upon which the successive eluates mentioned above are marked (Figure 1). By connecting these points a curve is obtained, each elevation of which corresponds to a 17-ketosteroid.

Using normal urine seven such elevations are obtained which indicates that normal urine contains at least seven different 17-ketosteroids. The possibility cannot be excluded that two or more different 17-ketosteroids are eluated simultaneously thus leading to a concurrent elevation in which case more than seven different 17-ketosteroids may be present in normal urine.

We have allotted Roman numerals to the various elevations. In order to explain why we skip the number II in the graph for normal urine we have to anticipate some of the results reported below in this paper. The

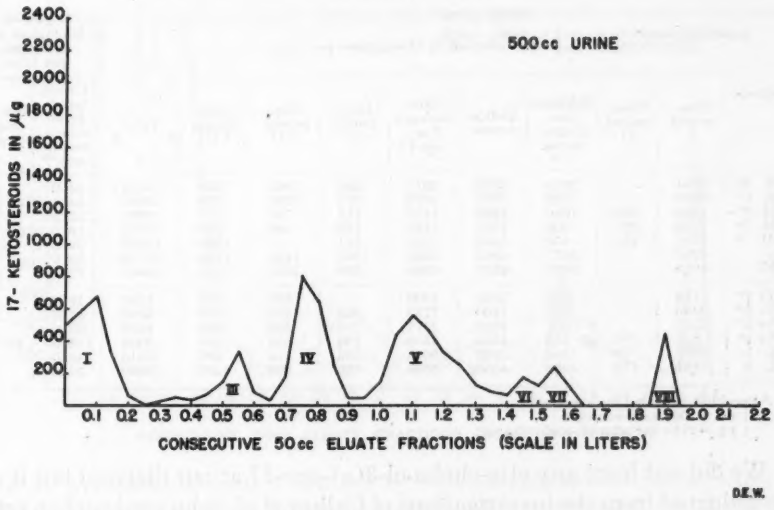

FIG. 1. 17-Ketosteroid pattern obtained by chromatographic-colorimetric analysis of 500 cc. of urine from a normal woman.

analysis of the urine from sufferers from adrenal dysfunctions often yields a curve with eight instead of seven elevations. This additional elevation lies between I and III and has been given the number II.

C. Identification of the different known urinary 17-ketosteroids

So far as we know, five different 17-ketosteroids have been demonstrated in urine of normal persons, *i.e.*, androsterone [Butenandt (3); Callow (4, 6, 7)], dehydro-iso-androsterone [Butenandt (2); Callow (5)], etio-cholanol-3(α)-one-17 [Callow (4)], iso-androsterone [Pearlman (17)], androstenone-17 [Dobriner (10)].

In order to find out which elevations are caused by these substances a known amount (usually 2 mg.) is added to one half of the urinary extract. Both halves of the extract, the one with and the one without the addition, are subjected separately to chromatographic analysis. In this way it can be verified that the Elevation III is caused by dehydro-iso-androsterone whereas the Elevation IV is due to androsterone. Unfortunately the elevation produced by iso-androsterone coincides with that of dehydro-iso-androsterone. These two substances are difficult to separate, particularly since both are precipitated by digitonine.

TABLE 1. NORMAL ADULTS

Initials	17-Ketosteroids in Micrograms per Liter									Biological Activity in I.U. per Liter	
	Compound I	Compound II	Dehydro-iso-androsterone	Androsterone	Etio-cholanol-3(α)-one-17	Compound VI	Compound VII	Compound VIII	Total	Calculated from colorimetric assay**	Capon comb assay
♂H 2*	3644	—	2018	3660	3910	580	960	710	15482	44.0	40
H 1*	3984	—	1326	2966	1670	970	1760	820	13496	34.5	35
M 2*	1208	208	1049	1880	1476	119	734	315	6989	22.5	±25
M 1*	1348	221	804	1591	1475	148	460	286	6333	19.0	±25
dV *	2791	433	850	3608	2936	341	—	1586	12545	39.0	>30
S	4264	—	3472	4562	8200	1500	1480	1280	24758	58.0	—
N	2910	—	3036	6812	6586	580	1350	1188	22462	77.0	—
♀Vr 1*	2118	—	656	1653	1900	—	830	426	7583	19.0	20
Vr 2*	2450	—	972	1400	1739	663	324	648	8196	17.5	20
Vr 3*	2231	—	707	1924	2271	220	620	666	8639	22.0	25
Vr 4*	895	186	818	1553	1554	280	683	630	6599	18.5	20–25
L 1	2500	238	1344	3956	5048	532	812	886	15316	45.0	—
L 2	2484	476	3288	4036	5548	468	960	1200	18460	52.0	—

* Specimen collected during wartime.
** 1 I.U. = 100γ androsterone.
1 I.U. = 275γ dehydro-iso-androsterone.

We did not have any etio-cholanol-3(α)-one-17 at our disposal but it can be deducted from the investigations of Callow *et al.*, who used carbon tetrachloride as an eluant, that Elevation V is caused by this substance. Work is in progress to identify the steroids which cause the Elevations I, VI, VII and VIII.

D. 17-Ketosteroid analyses of urines from normal persons

In Table 1 the results of the analyses for 17-ketosteroids in the urine of normal adults have been compiled. Some of the specimens used were obtained from one person only, some were taken from pooled urines. Whenever possible the total urine voided over a 24-hour period was collected. The quantities of 17-ketosteroids are listed in micrograms per liter.

A comparison of the total quantity of 17-ketosteroids in the urines collected during the war with that in post-war specimens shows a rise in the latter. One of the reasons for this difference lies in the fact that the volume

of urine eliminated during the years of war was 1½ to two times that during normal periods. Besides, there is a possibility that the inadequate or unbalanced diet with its preponderance of carbohydrates which prevailed for many years depresses the excretion of 17-ketosteroids.

The results show that during the war the total excretion of 17-ketosteroids varied between 6.3 and 15.4 mg. per liter. The corresponding figures obtained after the war are 22.4 to 24.7 mg. per liter for two men and 15.3 to 18.5 mg. per liter for a woman. This data affords a comparison with that of other investigators who did not further fractionate the 17-ketosteroids. The assay of the total content of 17-ketosteroids, while permitting

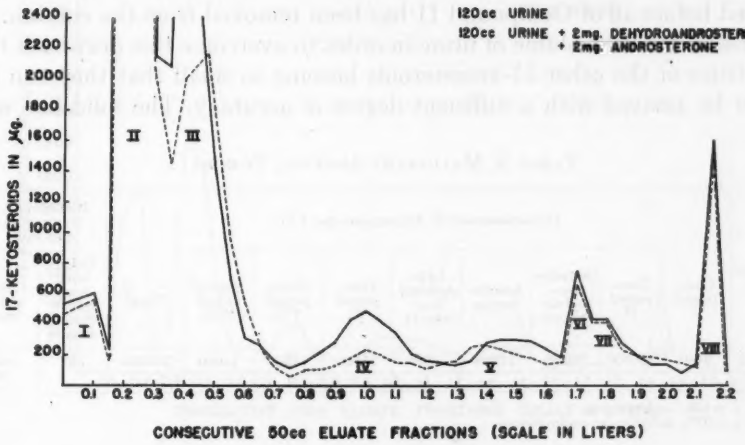

FIG. 2. 17-Ketosteroid pattern obtained by chromatographic-colorimetric analysis of 120 cc. of urine from patient with malignant adrenal tumor. The peak of Elevation II is omitted because it is too high (13,000 μg).

a quantitative differentiation between urine of normal persons and of those with various disorders, does not disclose any qualitative differences.

It can also be calculated from Table 1 that the ratio [dehydro-iso-androsterone:androsterone] varies between 0.24 and 1.0 and averages 0.5. The ratio [androsterone:etio-cholanol-3(α)-one-17] is 1 with some exceptions.

The androgenic activity of several urines was also assayed by the capon comb test. There is good agreement between the colorimetric and the biologic assay (Table 1). The biological activities of androsterone and dehydro-iso-androsterone used in the calculations are given in the table. They surpass by far those of any of the other known 17-ketosteroids.

E. 17-Ketosteroid analyses of urines from patients with various disorders

1. Malignant adrenal tumor

A female, 42 years old, was suspected of having an adrenal neoplasm. Patient died two weeks after specimen was received; post-mortem examination revealed hypernephroma. Since 1,400 I.U. or more of androgen per liter had been observed biologically in the urine of patients suffering from malignant adrenal tumors, large quantities of 17-ketosteroids were expected in this case, and therefore only 120 and 60 cc. respectively of urine were used in the analyses.

Figure 2 is the graph obtained in the analysis of 120 cc. In spite of the small volume of urine used the amount of the 17-ketosteroid II and of dehydro-iso-androsterone is so large that some of the latter begins to be eluated before all of Compound II has been removed from the column. If one uses a smaller volume of urine in order to overcome this drawback the quantities of the other 17-ketosteroids become so small that they can no longer be assayed with a sufficient degree of accuracy. The solid line was

TABLE 2. MALIGNANT ADRENAL TUMORS

Initials	Age	17-Ketosteroids in Micrograms per Liter									Biological Activity in I.U. per Liter	
		Compound I	Compound II	Dehydro-iso-androsterone	Androsterone	Etiocholanol-3(α)-one-17	Compound VI	Compound VII	Compound VIII	Total	Calculated from colorimetric assay*	Capon comb assay
Go	42	9440	180500	70200	11200	14000	21500	13500	14000	334340	367	>400 600

* 1 I.U. = 100γ androsterone.
1 I.U. = 275γ dehydro-iso-androsterone.

obtained after the addition of 2 mg. of dehydro-iso-androsterone and 2 mg. of androsterone to the extract from another 120 cc. of urine. This proved that dehydro-iso-androsterone and androsterone actually correspond with the Elevations III and IV.

This table shows the presence of 180 mg. of Compound II per liter, a substance of which only traces occur in normal urine. There is also a substantial increase in dehydro-iso-androsterone excretion, from the normal average of 1–3 mg. to 70 mg. All the other 17-ketosteroids are also increased in amount although to a lesser degree than those mentioned. The ratio [dehydro-iso-androsterone:androsterone] is 6.25, as compared with 0.5 for normal urine. Calculations based on the colorimetric assay showed a total amount of 367 I.U. of androgens per liter. This compares favorably with the results of the capon comb assay—>400 I.U., but <600 I.U. per liter.

The estrogen assay showed 7,000 I.U. per liter.

2. Another group of patients showing similar although less pronounced deviations are the intersexes (pseudohermaphrodites). According to the chromatographic pattern these patients can be divided into two groups. In one group the elevations resemble greatly those found in patients with adrenal tumors, whereas in the other group the 17-ketosteroids excreted are qualitatively and quantitatively indistinguishable from those of normal specimens.

Patients belonging to the former group have symptoms of virilism, and

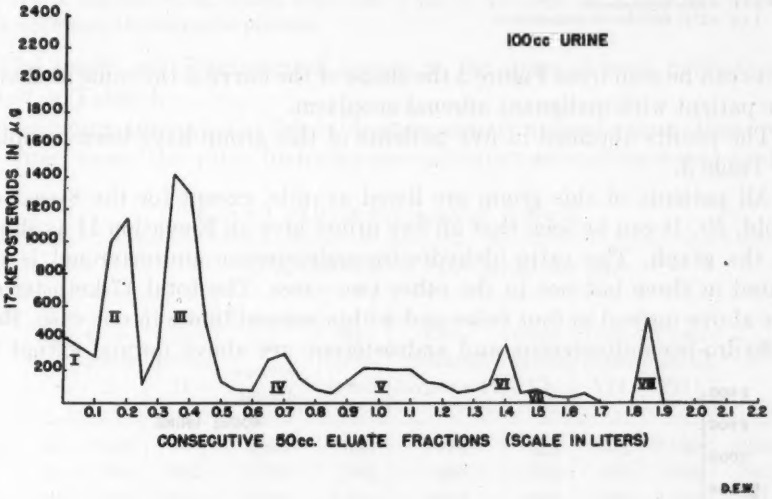

FIG. 3. 17-Ketosteroid pattern obtained by chromatographic-colorimetric analysis of 100 cc. of urine from a female intersex (type A).

one or both of their adrenals may be enlarged. In two of the cases in Table 3 (*Br.* and *Bo.*) one of the adrenals was removed. The extirpated adrenal of the 8-year-old boy, *Br.*, weighed 22 gm., while that of the 24-year-old girl, *Bo.*, weighed 44 gm. A few females of the second group do not show virilism.

Figure 3 is a curve representing the 17-ketosteroids belonging to the first group of intersexes.

Ha$_1$. is a girl of 16 years with external masculine pseudohermaphrodism. She has male characteristics including hirsutism on the abdomen, legs, and face, and her voice is deep. Her external genital organs consist of a hypospadic penis. No gonads can be detected and there is no scrotum. The urethral orifice is perineal.

TABLE 3. FEMALE INTERSEXES—TYPE A

Initials	Age	17-Ketosteroids in Micrograms per Liter									Biological Activity in I.U. per Liter	
		Compound I	Compound II	Dehydro-iso-androsterone	Androsterone	Etiocholanol-3(α)-one-17	Compound VI	Compound VII	Compound VIII	Total	Calculated from colorimetric assay*	Capon comb assay
Ha	16	5350	23710	37680	8860	12920	5800	2600	5140	102060	226	—
Br	8	5621	4200	5879	6405	10249	4144	12431	5066	53994	85	± 100
Bo	24	1963	5393	6890	5040	10287	1607	8273	4143	43596	75	± 100
Li	?	2560	19290	1546	2262	1734	2544	1648	3136	34720	29	± 100
Mo	39	5800	2635	8575	19720	22080	6275	12880	7105	85070	228	—

* 1 I.U. = 100γ androsterone.
1 I.U. = 275γ dehydro-iso-androsterone.

As can be seen from Figure 3 the shape of the curve is the same as that of the patient with malignant adrenal neoplasm.

The results obtained in five patients of this group have been compiled in Table 3.

All patients of this group are listed as girls, except for the 8-year-old child, *Br*. It can be seen that all five urines give an Elevation II as shown in the graph. The ratio [dehydro-iso-androsterone:androsterone] is elevated in three but not in the other two cases. The total 17-ketosteroids are above normal in four cases and within normal limits in one case. Both dehydro-iso-androsterone and androsterone are above normal except for

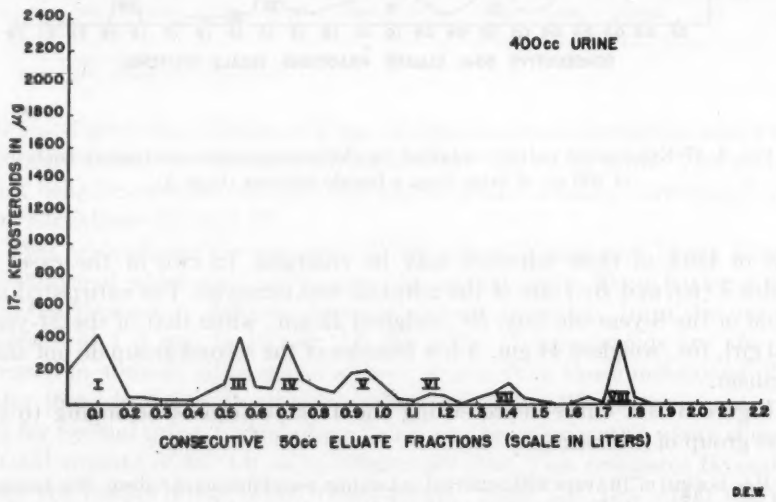

FIG. 4. 17-Ketosteroid pattern obtained by chromatographic-colorimetric analysis of 400 cc. of urine from a female intersex (type B).

Case 4, which constitutes an exception in this table since it is only the Elevation II which distinguishes this specimen from those of normal persons.

The pattern of 17-ketosteroid excretion of the second group of intersexes is exemplified by Figure 4.

Miss de G., 21 years old, has had no menarche; her appearance and hair distribution are female. The borderline of the pubic hair is horizontal and the clitoris is normal. The labia minora are somewhat too small. The vestibulum is approximately normal. No vagina seems to exist, and upon rectal examination a small knob of tissue can be felt, the size of the nail of the fourth finger and ½ cm. in thickness. It is uncertain whether this represents the uterus or prostate.

The results of 17-ketosteroid assays on the urine of such patients are listed in Table 4.

The figures presented in this table approximate normal values. However, in three cases the ratio [dehydro-iso-androsterone:androsterone] is increased but rather because of a low androsterone than of a high dehydro-iso-androsterone value. The ratio [androsterone:etio-cholanol-3(α)-one-17] again is approximately one.

TABLE 4. FEMALE INTERSEXES—TYPE B

Initials	Age	17-Ketosteroids in Micrograms per Liter								
		Compound I	Compound II	Dehydro-iso-androsterone	Androsterone	Etio-cholanol-3(α)-one-17	Compound VI	Compound VII	Compound VIII	Total
deGr	20	2520	—	2023	1968	1470	325	808	1130	10244
vR	13	320	892	2552	786	866	860	460	906	7642
Mu	19	813	1822	2730	1514	2018	1804	698	1522	12911
Ke	19	1532	—	643	1865	2625	?	?	?	?

The urine of patient *Mu.* yields a curve with a rather pronounced Elevation II in contrast to the pattern of Figure 4. It therefore constitutes a borderline case between the two groups of intersexes described above. This patient has some beard growth and an enlarged clitoris but otherwise has in general a female appearance.

Table 5 shows the results of 17-ketosteroid analysis of the urine of boys diagnosed as suffering from precocious puberty.

Patient Ha_2., eight years of age, is a brother of patient Ha_1. described above, the group of female intersexes, type A (Figure 3 and Table 3). The other boy, 14 years of age, had precocious puberty with gynecomastia. This boy underwent a change in psychic char-

acteristics at the age of nine, coincident with his precocious sex development and abnormal growth.

Considering his age the total amount of urinary 17-ketosteroids of patient *Ha*$_2$. is high (37.5 mg. per liter), but there is no Elevation II. Both dehydro-iso-androsterone and androsterone are above normal but their ratio is within normal limits. The graph for the urine of patient *Ro* differs from all the others by the absence of both Elevation VI and VII. No explanation can be offered for this at the present time.

F. Elevation II

One of the first problems arising from the examination of the graphs

TABLE 5. PRECOCIOUS PUBERTY—BOYS

Initials	Age	17-Ketosteroids in Micrograms per Liter								
		Compound I	Compound II	Dehydro-iso-androsterone	Androsterone	Etiocholanol-3(α)-one-17	Compound VI	Compound VII	Compound VIII	Total
Ha$_2$	8	7403	—	4750	7950	7070	6017	3853	923	37966
Ro	14	1216	—	763	2206	1291	—	—	1035	6511

and tables is the identity of the 17-ketosteroid causing Elevation II in the urine of patients with adrenal hyperfunction.

Dorfman, Schiller and Sevringhaus (11) reported the isolation of androstenol-3(α)-one-17 from the urine of a girl suffering from virilism. This substance seems to be identical with that isolated by Wolfe, Fieser and Friedgood (20) from the urine of a girl suffering from a malignant adrenal tumor. These authors suggested that their androstenol-3(α)-one-17 is a C_3 epimer of the androstenol-3(β)-one-17, obtained by the dehydration of a substance derived from one of the cortical steroids with a hydroxy group at C_{11}. Dorfman *et al.* assume that this androstenol-3(α)-one-17 is an artefact caused by the HCl hydrolysis of the urine, with a double bond at C_{11}, either $\Delta^{9,11}$ or $\Delta^{11,12}$.

Mason (15) reported the isolation of androstanediol-3(α)-11(β)-one-17 from the urine of three women with adrenal tumors, three "hermaphrodites" and one boy with adrenal hyperplasia.

Miller, Dorfman and Sevringhaus (16) reported the isolation of the same compound from the urine of a patient with virilism. This substance yielded upon dehydration androstenol-3(α)-one-17, as mentioned above.

We invariably encounter Elevation II upon chromatographic analysis

of the urines of patients with adrenal dysfunction (including malignant adrenal tumors), and virilism, and intersexes with virilism.

In view of the above reports we consider it likely that Elevation II is caused by androstanediol-3(α)-11(β)-one-17. Heating this Compound II with Girard's reagent leads to an increase of Elevation I and simultaneously to a disappearance of Elevation II. This does not necessarily imply that the new compound formed is identical with that causing Elevation I in all urine extracts.

Subjecting Compound II under comparable conditions to glacial acetic acid in absolute ethanol instead of to Girard's reagent also results in the disappearance of Elevation II and a coincident increase of Elevation I. Glacial acetic acid and hydrochloric acid seem to have a dehydrating effect and to produce androstenol-3(α)-one-17.

G. $\Delta^{3,5}$-androstadiene-one-17

Burrows *et al.* (1) found, in the urine of a patient with a malignant adrenal tumor, $\Delta^{3,5}$-androstadiene-one-17 which does not occur in the urine of normal persons. These authors suggest that this compound results from HCl hydrolysis of the urine. They succeeded in preparing $\Delta^{3,5}$-androstadiene-one-17 by dehydration of dehydro-iso-androsterone with the aid of $CuSO_4$. We investigated the action of aqueous HCl (2.5 per cent) upon dehydro-iso-androsterone by heating the mixture for from $\frac{1}{4}$ to 6 hours. This treatment converts a considerable part of dehydro-iso-androsterone into $\Delta^{3,5}$-androstadiene-one-17 while another part is converted into a substance which is not a 17-ketosteroid since it no longer gives the Zimmermann reaction. Heating the dehydro-iso-androsterone mixture for three hours on the waterbath will convert 40 per cent into $\Delta^{3,5}$-androstadiene-one-17. Under the conditions set up by Burrows *et al.* it is obvious that much if not all the dehydro-iso-androsterone would undergo transformation.

Our investigations have shown furthermore that the method of hydrolysis which we use with urine (simultaneous hydrolysis and extraction) results in the conversion of 3 per cent dehydro-iso-androsterone into $\Delta^{3,5}$-androstadiene-one-17. These substances were separated chromatographically and were subsequently assayed colorimetrically. This work will be reported elsewhere.

It is most probable that $\Delta^{3,5}$-androstadiene-one-17 as isolated by Burrows *et al.* from the urine of a patient with a malignant adrenal tumor is an artefact obtained by the conversion of dehydro-iso-androsterone.

This explains why with the same method of extraction no $\Delta^{3,5}$-androstadiene-one-17 was found in the urine of normal persons in which the amounts of dehydro-iso-androsterone are much smaller.

The amount of dehydro-iso-androsterone found in the urine of normal persons ranges in our series from 1 to 3 mg. per liter, whereas 70 mg. per liter could be demonstrated in the urine of a patient with a malignant adrenal tumor.

H. Elevation I

In discussing which substance is most likely to cause Elevation I in all urine extracts, it should be remembered that a non-alcoholic ketone Δ^2- or Δ^3-androstenone-17 has been found by many investigators in urine extracts. Hirschmann (13) obtained androstenone-17 from the urine of ovariectomized women. Pincus and Pearlman (18) obtained similar compounds from various human urines. Hoffman (14) found androstenone-17 in the urine of a patient with a malignant interstitial cell tumor and Dobriner *et al.* (9) isolated androstenone-17 from the urine of normal men and women. According to Venning, Hoffman and Browne (19) esterified androsterone is partially converted upon hydrolysis into androstenone-17, in contradistinction to free androsterone. Chromatographically Fish *et al.* (12) found androstenone-17 in the first eluates. It is therefore most likely that our Elevation I is caused by androstenone-17.

I. Discussion

In spite of shortcomings of our method of differential assay of various 17-ketosteroids, we believe that this method is preferable to the determination of the total 17-ketosteroids and also to the biological assay.

The advantages over the assay of the total 17-ketosteroids are:

1. The chromatographic-colorimetric analysis of urinary extracts results in a graph from which qualitative, in addition to quantitative, deviations from the normal become evident.

2. The ratio [dehydro-iso-androsterone:androsterone] holds promise of being significant in the diagnosis of adrenal and probably also of gonadal dysfunction.

The advantages over the biological assay are:

1. The chromatographic-colorimetric analysis is less expensive to use.

2. It is less time-consuming.

3. The assay can be carried out with as little as half a liter of urine, which makes daily analysis feasible if necessary.

At the time of writing we are unaware of any routine clinical analysis of individual 17-ketosteroids carried out elsewhere. Chromatography has been used previously for the separation and purification of 17-ketosteroids in extracts of urine which had been collected over a long period of time.

Disadvantages of our method are the time required for the analysis and the fact that the elevations caused by iso-androsterone and dehydro-iso-androsterone coincide. This is the more disappointing as both compounds

have trans-configuration and can therefore not be separated by digitonine. A method of separation is under investigation. The assay of fractions I and VIII are not accurate, since these eluates are yellow to brown in color because of impurities and they become turbid on addition of the reagent. Unfortunately we cannot use Girard's reagent for the purification of extracts of urine from patients because this impairs Elevation II, and we must therefore use cruder extracts for the chromatography.

SUMMARY

1. A chromatographic-colorimetric analysis of urinary extracts from normal persons yields a graph with seven elevations.

The total amount of 17-ketosteroids in man tested during the war-time period varied within a range of from 6.3 to 15.4 mg. per liter of urine. The corresponding post-war values for men are: 22.4 to 24.7 mg. per liter, and for women: 15.3 to 18.5 mg. per liter.

The ratio [dehydro-iso-androsterone:androsterone] ranges within 0.24 to 1 with an average of 0.5. The ratio [androsterone:etio-cholanol-3(α)-one-17] is about one.

2. The graph obtained for the urinary 17-ketosteroids of a woman suffering from a malignant adrenal tumor shows eight instead of seven elevations. The compound causing the additional elevation (II) is probably androstanediol-3(α), 11(β)-one-17, and amounted in this specimen to 180 mg. per liter of urine. All the other 17-ketosteroids are present at levels higher than normal, particularly dehydro-iso-androsterone. The ratio [dehydro-iso-androsterone:androsterone] is raised to 6.25.

3. Intersexes can be subdivided into two groups:

a. Patients with hirsutism or virilism

Urinary 17-ketosteroid graphs of this group of patients resemble qualitatively those of patients with adrenal malignancy: presence of Elevation II; high ratio of [dehydro-iso-androsterone:androsterone]; high level of the biologically active steroids dehydro-iso-androsterone and androsterone.

b. Patients without hirsutism or virilism

Urinary 17-ketosteroid graphs of this group of patients resemble qualitatively those of normal persons. The total amounts of dehydro-iso-androsterone and androsterone (which are responsible for the biologic activity of the extracts) are rather below normal. The ratio [dehydro-iso-androsterone:androsterone] is similar to that of normal specimens or sometimes higher because of a level of androsterone lower than in normal persons.

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TESTOSTERONE PROPIONATE THERAPY IN ONE HUNDRED CASES OF ANGINA PECTORIS

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IN PREVIOUS communications (3, 4), the beneficial effects of testosterone propionate therapy in 46 patients with angina pectoris have been reported. The present report is based on a series of 100 consecutive patients with angina pectoris who have received this form of therapy. They have been followed over periods varying from several months to as long as five years.

Care was exercised in the choice of patients. No patient was treated unless the diagnosis of angina pectoris was clearly established. This diagnosis was based on a history of typical attacks of substernal or precordial pain precipitated by exertion or emotion and relieved by rest or nitroglycerin. In many of these patients, the pain radiated to one or both arms, shoulders, back or jaw.

METHOD AND RESULTS

One hundred patients with angina pectoris, 92 men and 8 women, ranging from 34 to 77 years in age, received testosterone propionate therapy.[1] Ninety-one showed moderate to marked improvement, while 9 had no noticeable beneficial effects. Of the 91 patients who showed improvement, 51 had marked and 40 moderate beneficial results. A patient was classified as showing "marked improvement," if he was able to increase his physical activity without precipitating an anginal attack for a period of at least 2 months after testosterone therapy was discontinued. A patient was considered to have "moderate improvement" if the anginal attacks were reduced to less than half the number he had prior to treatment. Those patients in whom there was no noticeable reduction in the number of attacks following this form of therapy were considered "failures." Of the 92 men, 49 showed marked and 36 moderate improvement. Seven men showed no change. Of the eight women treated, two showed marked, four moderate, and two no noticeable improvement (Table 1). Neither the age of the patient nor the duration of the angina pectoris had any bearing on the re-

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[1] Kindly supplied by Ciba Pharmaceutical Products, Incorporated, Summit, New Jersey, under the trade name of *Perandren*.

sults obtained. The older patients, both from the point of view of age and duration of the disease, showed as good a response to testosterone therapy as did the younger patients.

The improvement after the use of this hormone varies with the individual both in time of onset and in degree. Whereas some patients showed improvement after the second or third injection of testosterone propionate, there were others in whom no improvement was noted until the eighth, ninth, or tenth injection. Some required as many as 15 to 25 injections over a period of from four to five months before therapy could be discontinued. These considerations emphasize the importance of studying each patient carefully and giving him an adequate course of treatment.

TABLE 1. SUMMARY OF RESULTS OBTAINED IN THE TREATMENT OF 100 CASES OF ANGINA PECTORIS WITH TESTOSTERONE PROPIONATE

	Marked improvement	Moderate improvement	No improvement
Males	49	36	7
Females	2	4	2
Totals	51	40	9

It is difficult to evaluate with certainty any form of therapy in the syndrome of angina pectoris inasmuch as patients have been known to improve spontaneously, as well as with various forms of medication. Therefore, to control the studies carried out with testosterone propionate, one group of seven patients was treated with placebo medication prior to testosterone propionate therapy and a second group of four patients was studied by means of the two-step test designed and described by Master and Oppenheimer (6). Furthermore, the effect of seasonal conditions has been fully considered in the evaluation of the results obtained, and most of the patients were treated during the fall and winter months at a time when climatic conditions made them more subject to anginal attacks.

To eliminate the psychological effect of injection therapy *per se*, five patients were given six consecutive injections of sterile sesame oil prior to receiving testosterone propionate, and two were similarly controlled after a recurrence of anginal symptoms following the first course of the drug. None of the patients who had received sterile sesame oil alone showed any appreciable change in symptoms. On the other hand, progressive improvement was noted in these same patients following the use of testosterone propionate. The contrast was particularly striking in two patients who were first treated with testosterone propionate with marked improvement,

and then had a recurrence of symptoms four and seven months respectively after the last injection. For these new attacks, they were given placebo injections of sterile sesame oil, without clinical improvement. Following a return to testosterone therapy, relief from anginal attacks was again obtained.

The four patients studied by means of the two-step test before and during the course of testosterone therapy present objective evidence of improvement under this regimen. The exercise-tolerance tests were performed under standardized conditions—approximately 2 hours after meals, at a fairly constant rate of speed, and at a room temperature of 72 (± 4)° F. An average of 28 days passed before objective improvement was noted, and a period of 43 days elapsed before this improvement became marked.

TABLE 2. RESULTS OF EXERCISE TOLERANCE TESTS IN 4 PATIENTS TREATED WITH TESTOSTERONE PROPIONATE
(25 mg. per dose)

Patient	Number of injections		Days		Total number injections	Duration of therapy (days)	Number of trips*		Duration of pain† (seconds)	
	Before subjective improvement	Before quantitative improvement	Before subjective improvement	Before quantitative improvement			Before therapy	After therapy	Before therapy	After therapy
E.W.	3	6	14	26	16	87	39	82	169	55
W.W.	3	8	14	32	12	57	39	71	92	38
B.M.	2	6	5	33	10	78	43	76	45	24
J.W.	4	6	14	21	14	63	27	47	72	46

* Trips—average of 3 tests preceding inception and cessation of therapy.
† Pain—average of 3 tests preceding inception and cessation of therapy.

The results have been reported in a previous communication (4) and are summarized in Table 2.

Fluoroscopic examinations, serial kymograms, and electrocardiograms revealed no uniform changes resulting from this therapy. Recently, Waldman (14) reported that the depressed S-T segments which have been observed in patients with angina pectoris following exercise-tolerance tests assumed a more normal contour with testosterone propionate therapy. It can be expected that signs of this nature, if found to be significant enough and established in a large series of individuals, may supply a satisfactory guide for the management of angina pectoris patients with testosterone propionate relative to dosage, frequency of injections and termination of treatment.

CASE REPORTS

These two case reports are follow-up histories of patients reported in a previous communication (4) and are presented to point out that testos-

terone propionate therapy may be followed by persistent beneficial effects for as long as 26 to 34 months after treatment has been discontinued.

Case 1. E.W., a 57-year-old grocery clerk, had a history of angina pectoris of 6 months' duration, during which time he was unable to work. The pain was substernal in location and was relieved by rest or nitroglycerin. Physical examination revealed a blood pressure of 140/80 mm.Hg. The heart was not enlarged, there were no murmurs or thrills, and the rate and rhythm were normal. The heart sounds were poor in quality. The electrocardiogram and sedimentation rate were within normal limits.

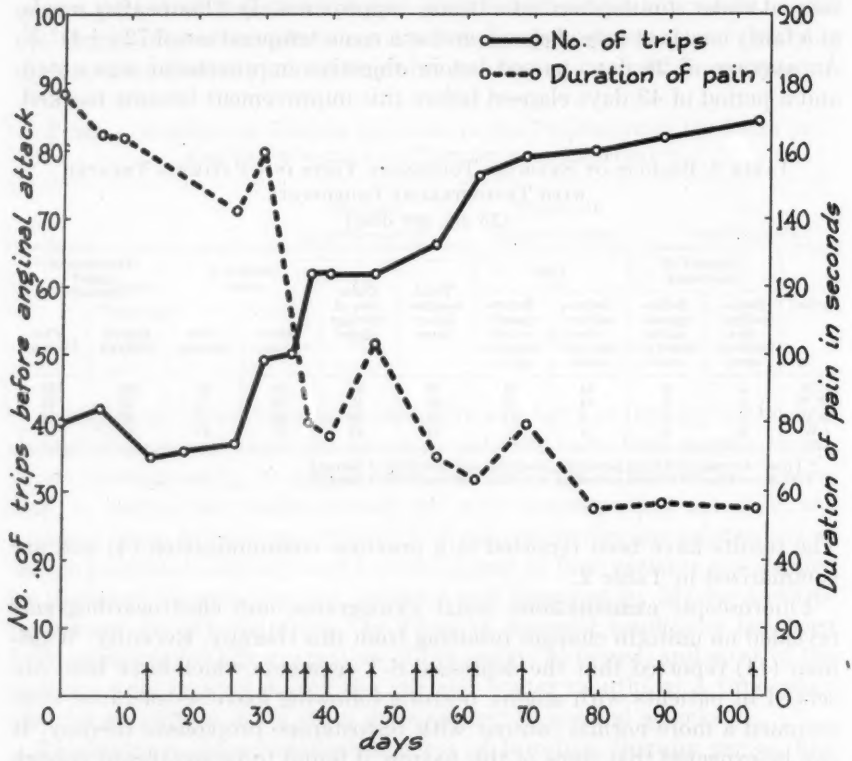

FIG. 1. The effect of testosterone propionate therapy on exercise tolerance and duration of anginal pain in patient, *E.W.* Each arrow represents one injection of 25 mg. of testosterone propionate.

The exercise-tolerance tests prior to testosterone propionate therapy ranged from 35 to 42 trips, and the duration of substernal pain varied from 155 to 178 seconds. Definite subjective improvement was reported by the patient after the third injection. Objective improvement, however, did not

occur until after the sixth injection, and following the sixteenth treatment he was able to double his exercise before precipitating an attack. During this period, the severity of the attacks was decreased as measured by the duration of the pain, which fell from a maximum of 178 seconds to 55 seconds (Figure 1). Following the twelfth injection the patient returned to

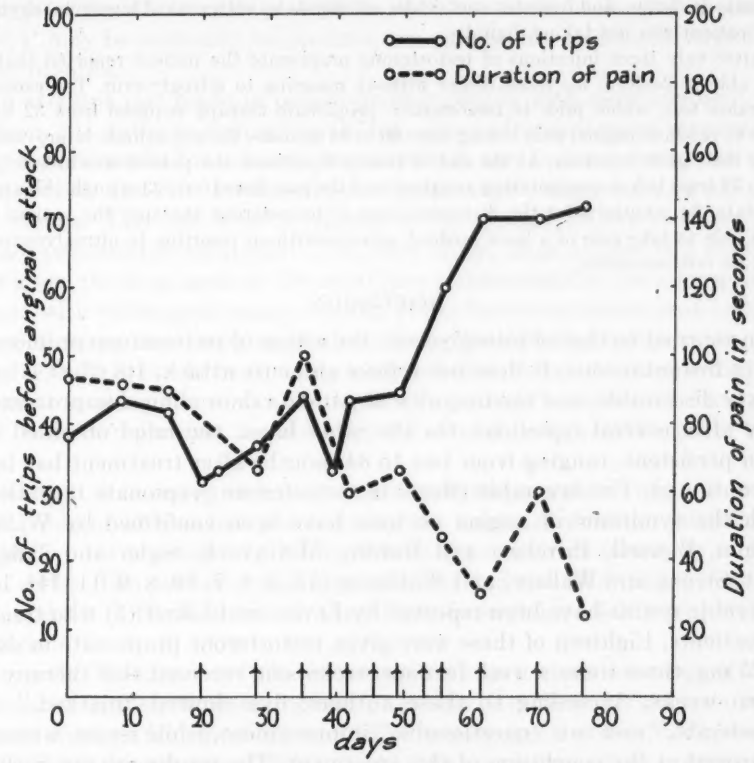

FIG. 2. The effect of testosterone propionate therapy on exercise tolerance and duration of anginal pain in patient, *W.W.* Each arrow represents one injection of 25 mg. of testosterone propionate.

work, and suffered no further attacks until 26 months later, when he again experienced substernal pain on exercise or emotion. He was given 25 mg. doses of testosterone propionate intramuscularly at weekly intervals for a period of 6 weeks when he again became free of anginal attacks. Following this second course of therapy, there has been no recurrence of anginal pain up to this time, a period of 12 months.

Case 2. W.W., a 64-year-old physician, had a history of angina pectoris of four years' duration. The pain, which was substernal and radiated down the left arm, was brought on by climbing one flight of stairs or by walking three or four city blocks, and was relieved by rest or nitroglycerin, of which from two to four tablets were required daily.

Physical examination revealed a blood pressure of 140/70 mm.Hg. The heart size was within normal limits, the sounds were fair in quality with a harsh systolic murmur at the base; no thrills were present. The electrocardiogram showed a high degree of left-axis deviation, and frequent ventricular extrasystoles with runs of bigeminal rhythm. The patient was not taking digitalis.

After only three injections of testosterone propionate the patient reported that he was able to perform his usual duties without resorting to nitroglycerin. The exercise-tolerance test, which prior to testosterone propionate therapy required from 32 to 43 trips to produce anginal pain lasting from 90 to 94 seconds, showed definite improvement after the eighth injection. At the end of twelve injections, the patient was able to perform 72 trips before precipitating an attack and the pain lasted only 23 seconds (Figure 2). To date, 34 months after the discontinuance of testosterone therapy, the patient has been able to take care of a busy medical practice without resorting to nitroglycerin except on rare occasions.

DISCUSSION

In contrast to that of nitroglycerin, the action of testosterone propionate is not instantaneous. It does not relieve an acute attack. Its effect is only slowly discernible, and the majority of patients show clinical improvement only after several injections. On the other hand, the relief obtained has been persistent, ranging from two to 34 months after treatment has been discontinued. The favorable effects of testosterone propionate in patients with the syndrome of angina pectoris have been confirmed by Walker, Hamm, Bonnell, Pritchett and Rardin, McGavack, Sigler and Tulgan, Opit, Strong and Wallace, and Waldman (15, 2, 1, 7, 10, 8, 9, 11, 14). Less favorable results have been reported by Levine and Likoff (5) who treated 19 patients. Eighteen of these were given testosterone propionate in doses of 25 mg. three times a week for four weeks; one received this therapy for seven weeks. According to these authors, five showed "marked," one "moderate," and two "questionable" improvement, while eleven were unimproved at the conclusion of this treatment. The results are not entirely at variance with those in this report. Approximately one third of our group showed no noticeable improvement during the first month of therapy. In our series, however, they did improve upon continuation of the testosterone therapy when given for a sufficient length of time. Objective studies have shown that an average of 28 days passed before definite improvement was noted and a period of 43 days elapsed before this improvement became marked.

Since it is impossible to measure accurately the degree of coronary impairment in a patient with angina pectoris, it is necessary to study each

case carefully, begin treatment conservatively, and gauge the frequency of injections according to the response of the patient. In the majority of individuals, 25 mg. of the drug was administered on the average of twice a week for the first two weeks, followed by weekly 25 mg. injections. The dosage, the time interval and the length of treatment varied with the individual patient. Some required as many as 15 to 25 injections, but the average of the whole series was 12. In order to obtain prolonged improvement it may be necessary to continue the therapy for as long as from five to six months.

An attempt was made to obtain quicker results with more frequent injections. Six patients were given 25 mg. doses of testosterone propionate daily for one week. Two showed improvement, two became worse, one was unimproved, and one developed acute pulmonary congestion and peripheral edema. The one who developed acute cardiac failure received no further testosterone treatment. The other three, after a lapse of a month, were given the drug again at the usual time intervals and in the appropriate dosage with subsequent improvement. It has been established that testosterone therapy can cause marked sodium, chloride and water retention (12, 13), and it can be reasonably assumed that the acute cardiac failure observed in one patient was the result of excessive testosterone therapy. This further emphasizes the necessity for careful dosage in the use of this drug.

Although it is recognized that spontaneous improvement may occur in some patients with angina pectoris over the course of weeks or months, it would be most unusual for this improvement to occur uniformly in such a large series. The persistence of improvement and the delay in its appearance make it difficult to believe that it can be explained solely on psychic grounds.

Recently Waldman (14) has summarized the various concepts of the mechanism of testosterone propionate therapy. Testosterone may act in a number of ways: by vasodilation of the coronary tree, by the development of a collateral coronary circulation, by the correction of an androgenic deficiency, or by an improved cardiac muscle metabolism. Pending further experimental and laboratory studies no definite conclusions on this phase of the problem can be drawn.

Testosterone propionate, properly used, not only reduces the frequency of attacks of angina pectoris, but decreases their severity when they do occur. Further time will be required for the evaluation of results before it can be determined definitely whether or not this treatment will prolong the life of the patient. These studies and those of others indicate that it will make him more comfortable and increase his capacity for work.

SUMMARY

One hundred patients with angina pectoris, 92 men and eight women, ranging from 34 to 77 years in age, have been treated during the last five years with testosterone propionate. Ninety-one per cent improved for periods ranging from 2 to 34 months.

In the majority of the patients, 25 mg. of the hormone was administered on the average of twice a week for the first two weeks, followed by weekly 25 mg. injections, with an average of 12 injections in the whole series.

No appreciable improvement was noted following control injections of plain sesame oil, although the same patients responded when placed on testosterone propionate therapy.

With appropriate dosage in the cases studied, no untoward effects were observed.

Four patients were studied by means of exercise-tolerance tests before and during the course of treatment to obtain objective measurements of their improvement. In each of these patients the amount of exercise which could be tolerated before the development of an anginal attack was markedly increased under testosterone therapy, and the severity of attacks, as measured by the duration of the pain, was correspondingly diminished. In each case, subjective improvement was reported before objective changes could be demonstrated by the test employed.

The summary of this larger series of cases of angina pectoris treated with testosterone propionate confirms the results previously reported.

ACKNOWLEDGMENT

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ADDISON'S DISEASE IN AN INFANT

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IN a recent review (2) of Addison's disease in children the reports of one hundred cases were analyzed. Sixty-two of these presented sufficient evidence to be classified as "proved." Only four cases under five years of age were found; three of these were associated with macrogenitosomia (1, 4, 5, 8, 9). The case study presented by Wilkins, Fleischmann and Howard (9) conclusively demonstrated that hyperplasia of the androgenic or fetal zone of the adrenals can be associated with insufficiency of the true cortical tissue. The other two similar cases were living at the time of the report and required specific therapy. The fourth case was a three year old girl, reported by Netter (4); the adrenal glands were found at autopsy to be destroyed by tuberculous lesions. Up to this time this was the youngest patient in whom tuberculosis was responsible for the disease.

The purpose of the present paper is to report the youngest recorded "proved" case of Addison's disease, and to describe the response of this girl, aged six and one-half months, to therapy with desoxycorticosterone acetate, with beef cortical extract, and with pork cortical extract.

Although simple atrophy cannot be disproved, it is probable that the case presented here is one of tuberculous involvement of the adrenals. If the etiological diagnosis is correct, this is not only the youngest patient with Addison's disease recorded, but the only reported living patient under twelve years of age (5) with this basis for the chronic adrenal insufficiency.

CASE REPORT

The parents were in good health. There was no family history of tuberculosis or syphilis. *M.E.T.* entered the St. Louis Children's Hospital on December 18, 1943, at 6½ months of age. She was an only child and had been born at full term, a normal delivery. She had been quite well until two months previously, when a cough and "stuffy nose" developed. Two days later a very high fever was noted, rapidly subsiding in three to four days with the appearance of a generalized macular rash. The rash faded in twenty-four hours, was not purpuric and the patient was not toxic. Prior to this time, she had always been very healthy and had eaten quite well; however, with the disappearance of fever, she began to lose desire for food; she lost weight, and became irritable. Two weeks later, her very fair skin was noted to be darker in color and periods of listlessness and drowsiness were frequent. At 5½ months of age, four weeks after the onset, projectile vomiting occurred once or twice daily, and there were occasional periods of diarrheal stools with mucus. The formula was changed a number of times, and one week before admission she received a blood transfusion without benefit. There had been

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no fever since the onset; there had been no convulsions, and the cough had disappeared. Although urination was frequent and in large quantities at the beginning of the illness, there was a definite history of oliguria during the past few weeks.

Physical examination revealed an obviously chronically ill and moderately emaciated infant. The weight was 6.35 kg. The skin was dehydrated, and presented a very faint "sun-tan like" discoloration. Not much attention was paid to this at the time because the mother and maternal grandmother had dark complexions similar to that of the child. The tongue, gingival and buccal mucous membranes were clear. Ears, nose and throat were normal and the lungs were clear. The heart was normal in size, good muscular quality, normal rate and rhythm. The liver edge was barely felt, spleen not enlarged and both lower poles of the kidneys were palpable, but appeared to be normal in size and consistency. The genitalia were those of a normal female infant. The rectal temperature was 36.6 degrees C. The systolic blood pressure was 90 mm. Hg., and the diastolic, 60 mm. Hg.

Laboratory findings on admission were: hemoglobin, 14.6 gm. per cent; leucocyte count, 20,350; differential leucocyte count revealed eosinophiles 1 per cent, stab forms 6 per cent, segmented forms 31 per cent, lymphocytes 51 per cent, and monocytes 11 per cent. The serum carbon dioxide combining power was 19 millimols per liter; non protein nitrogen, 80.5 mg. per cent; total serum protein, 6.73 gm. per cent. Blood serum agglutination tests for typhoid and paratyphoid infections were negative, and stool cultures revealed no abnormal bacteria or parasites.

The patient was given 400 cc. of lactate-Ringer's solution subcutaneously and 120 cc. of plasma diluted with an equal amount of 5 per cent glucose intravenously. Administration of parenteral fluids was repeated daily, and five days later the child was quite active, the appetite returned, the color was much better, hydration was restored, and the weight had increased from 6.35 kg. to 7.2 kg.

On January 3, 1944 the hemoglobin was 11.8 gm. per cent, erythrocyte count, 3,780,000 per cu. mm.; leucocyte count, 7,800 per cu. mm.; non-protein nitrogen, 33 mg. per cent; and total serum protein, 6.4 gm.; albumin, 4.66 gm.; globulin, 1.74 gm. During the period of hydration typical gastric waves were noted, and the patient vomited projectively a few times. The stools became formed and small in amount. The possibility of a partial high intestinal obstruction or pylorospasm was considered.

On January 3, a gastrointestinal x-ray series revealed an over-prompt motility with almost complete evacuation of the bowel within twenty-four hours.

Frequent examinations of the urine were negative. On a few occasions, the specific gravity ranged from 1.012 to 1.018. The ability to concentrate, the negative urine examinations plus the rapid fall of the non-protein nitrogen to normal following hydration were considered sufficient evidence to rule out disease of the kidneys as being the primary cause of this illness.

Because the child looked and acted so much better, and the mild generalized pigmentation of the skin noted on admission had almost disappeared, the idea of sending the patient home was entertained. However, forty-eight hours after parenteral fluids were discontinued, there was a weight loss of 400 grams. This was followed by a gradual refusal of food and the reappearance of dehydration.

On January 11, an intradermal tuberculin test was done, using 0.1 cc. of a 1:1000 dilution of old tuberculin. Almost immediately this produced marked induration, redness and exquisite tenderness of the arm nearly to the point of ulceration. A few days later the same test was repeated on the opposite arm with the same results. X-ray of the chest taken at this time showed haziness extending out and down from the right hilus,

and a thickening of the bronchial branches to both apices, most pronounced on the left. Dr. Sherwood Moore, our roentgenologist, thought this represented active pulmonary tuberculosis. In view of the absence of cough and stethoscopic findings, plus a markedly positive tuberculin test in an infant this age, this was considered to be an active but early or mild tuberculous infection. The possibility of a virus pneumonitis was not ruled out. Members of the immediate family were examined and found to be free of tuberculosis. It was eventually discovered that the colored house-man to whom the child may have been exposed, had a diffuse caseous tuberculous "honeycomb" destruction of the left lung, from which he expired a few months later.

On January 21, the non-protein nitrogen was 64 mg. per cent; carbon dioxide combining power was 22 millimols and serum chloride concentration was 89 milliequivalents per liter.

On January 28, fluids by mouth were denied in preparation for an intravenous pyelogram, and following this investigation, the child returned to her room in a state of mild shock and moderate dehydration. The pyelogram was interpreted as showing poor renal function because of the delay in diodrast excretion.

At this time the possibility of Addison's disease was seriously considered for the first time. Daily intramuscular injections of 2.0 mg. of desoxycorticosterone acetate were begun. Unfortunately, blood chemical determinations could not be done at this time, but on February 4, two days after resuming administration of parenteral fluids and the giving of "DOCA" the serum chloride was 99.6 milliequivalents per liter; the serum sodium was 130.5 milliequivalents per liter; and the serum potassium was 7.3 milliequivalents per liter. The chemical determinations were done in Dr. MacBryde's metabolism laboratory in Barnes Hospital, in which the normal ranges are: chloride, 99.2 to 106.0 milliequivalents per liter; sodium, 139.1 to 147.8 milliequivalents per liter; potassium, 4.6 to 5.6 milliequivalents per liter; bicarbonate, 25 to 27 millimols or milliequivalents per liter.

On February 7, the response to 5 minims of adrenalin subcutaneously was determined. The fasting c.w.b.t.[1] glucose was 20 mg. per cent; 20 minutes after adrenalin, 55 mg. per cent; 40 minutes, 35 mg. per cent; 60 minutes 20 mg. per cent; and 90 minutes, 17.0 mg. per cent. The patient showed no symptoms of hypoglycemia except lassitude and weakness.

On February 11, 5 cc. of whole beef cortical extract (Upjohn) was administered intramuscularly. Fasting c.w.b.t. glucose was 50 mg. per cent, after 1 hour, 55 mg., and after three hours, 57 mg. per cent.

On February 13 (on the advice of Dr. Cyril MacBryde), 0.5 cc. of pork adrenal cortex extract was given intramuscularly. The fasting c.w.b.t. glucose was 50 mg. per cent; 1 hour after injection, 72 mg. per cent; two hours, 59 mg. per cent; and three hours, 45 mg. per cent. It should be noted that there was a rise of 22 mg. per cent in the capillary blood glucose level after the injection of the cortical extract from hogs' glands, while after beef cortical extract the rise at one hour was only 5 mg. per cent. This is in agreement with the observations of MacBryde and De la Balze (3), who found that seven patients with Addison's disease exhibited a rise in capillary blood sugar when pork cortical extract was given, but that beef cortical extract gave comparatively little response. The doses used here (5 cc. of the beef extract and 0.5 cc. of the pork extract) represent

[1] c.w.b.t. means capillary whole blood "true" glucose. This method utilizes the zinc sulphate sodium hydroxide precipitating reagents of Somogyi (7) and the sensitive Shaffer-Somogyi (8) low blank reagent.

equivalent amounts of the two preparations in life sustaining properties; the pork extract preparation simply being 10 times as concentrated, but the pork cortical extract contains more of the compound E type of cortical fraction which influences carbohydrate metabolism.

By February 15, after 2.0 mg. desoxycorticosterone acetate had been given daily for twelve days, there was marked improvement. The skin gradually lost most of the pigmentation, the tissues filled out, the appetite was much better and for the first time the patient gained weight without parenteral fluids.

On February 22, the non-protein nitrogen was 40 mg. per cent; serum chloride, 107.8 milliequivalents per liter; sodium, 144.4 milliequivalents per liter; and potassium, 5.4 milliequivalents per liter. Concomitant with this improvement there was an increase in the fasting and four hour post-prandial blood sugar, the levels being 62 and 105 mg. per cent respectively. It was evident that whenever this child had her general strength restored by "DOCA" so that her appetite returned and she ate regularly, the blood glucose levels could be kept within fairly normal limits. As soon as regular food intake failed, hypoglycemia, listlessness and muscle weakness would appear.

On February 26, desoxycorticosterone was omitted for twenty-four hours and the patient became fussy, began to refuse food, became weak and listless and lost 150 grams of weight during the night. Daily administration of 2 mg. of "DOCA" was resumed, and she rapidly improved.

On March 3, x-ray examination of the chest was repeated and the pulmonary changes previously noted were still present, but to a lesser degree.

On March 12, the glucose tolerance test was: fasting c.w.b.t. glucose, 94 mg. per cent; ½ hour after 1.75 gm. glucose per kg., 163 mg. per cent; 1½ hours, 89 mg. per cent; 2½ hours, 65 mg. per cent; and 3½ hours 62 mg. per cent. For two weeks the patient had been running a low grade fever, from 37.4° C. to 38.0° C. The leucocyte count varied from 7,800 to 14,450 per cu. mm. with a relative increase in lymphocytes which varied from 62 to 80 per cent.

On March 14, the day of discharge, the weight was 8.35 kg. For the next six months the low grade fever continued without other constitutional signs or symptoms. Two mg. of "DOCA" were given daily. The pigmentation gradually became more noticeable, especially on the backs of the hands, dorsum of feet, groins and genitalia.

The many small, needle prick scars (from giving subcutaneous fluids along the side of the chest and about the ankles) became deeply pigmented, almost black in color. In addition, there was a progressive change in color of the buccal and gingival mucous membranes to a brownish-blue hue. The hair remained short, sparse, showing a tendency to become grey.

At 15 months of age, six months following discharge from the hospital, the weight had increased from 8.1 kg. to 11.8 kg., the height from 68.7 cm. to 81.2 cm., and eight new teeth had erupted. At 23 months, she began to walk, and as long as treatment was continued, to all appearances, she seemed perfectly normal for her age, with the exception of the pigmentation. The systolic blood pressure fluctuated from 100 to 120 mm. Hg.; the diastolic, from 60 to 70 mm. Hg. During this period the dose of desoxycorticosterone was varied from 1 to 2.0 mg. per day. With the 1 mg. dose, she became irritable and had a tendency to lose weight, but when it was increased to 2.0 mg. the disposition and weight gain returned to normal.

The patient at no time developed edema and the heart's size has remained within normal limits. She always had an excessive desire for table salt, and one teaspoonful daily, approximately 5 gm., was given in addition to the salt used in seasoning the foods.

A diet high in carbohydrate and protein was given, and large amounts of all known vitamins were prescribed.

The patient left St. Louis on September 29, 1944, and was again seen on May 17, 1945. During the interim she had been quite strong and active. The height was 91.2 centimeters; weight, 15.0 kg.; the skin pigmentation was extreme, almost "negro" black over the exposed surfaces, areolae of nipples and genitalia. The hair was still light grey in color, short and sparse, and the mucous membranes a deeper bluish hue. The blood pressure was 110/70 mm. Hg.; the teeth numbered fourteen, and had good structure. Her physical activity and mental reactions were normal for a two-year-old. Two mg. of desoxycorticosterone acetate daily were still required. The lungs were clear to roentgenological examination and an x-ray of the abdomen failed to reveal evidence of adrenal calcification.

The patient was in Miami, Florida, all summer and winter and remained in wonderful health. Because of her excellent physical condition, her mother gradually reduced the desoxycorticosterone acetate to 1.0 mg. daily, but at the same time the child was permitted to take all the additional table salt desired, and this varied between one and three teaspoonsful daily.

On December 2, 1945, the patient retired after eating only a fair evening meal. She awoke feverish in the early morning, and vomited twice. She refused breakfast and took very little liquid. By 2:30 P.M. that day the temperature was normal, but she was very listless. At 3:00 P.M. a generalized convulsion developed following which she lapsed into a comatose state. Emergency therapy was given in the nearest hospital, and immediately following the intravenous administration of 5 per cent glucose in normal saline the patient became alert and wanted to eat. Unfortunately, no blood chemistry determinations were made.

Following this, the "DOCA" was increased to 1.5 mg. daily. The course was uneventful until February 9 when she again became very weak following a period of refusal of food and salt. During this episode there was a sudden loss of weight of from two to five pounds in a twenty-four hour period.

On February 15, 1946, she was readmitted to St. Louis Children's Hospital. The child did not appear to be ill, but was listless and apprehensive. Her mental and physical development were much advanced over that of the average 2½ year old child. Teeth were twenty in number; height, 101.2 cm.; weight, 18.7 kg. The blood pressure was 80/50 mm. Hg. The generalized pigmentation was somewhat less marked, but the hair remained sparse, short, dry, and silver in color. Chemical measurements revealed that the carbon dioxide combining power was 21 millimols per liter; the non-protein nitrogen, 30 mg. per cent; the total serum protein, 6.39 gm. per cent; the serum calcium, 10.2 mg. per cent; the serum inorganic phosphorus, 4.6 mg. per cent; the serum sodium, 135 milliequivalents per liter; the serum potassium, 6.9 milliequivalents per liter; the serum chloride, 108 milliequivalents per liter.

On February 18, a standard glucose tolerance revealed: fasting blood sugar 47.8; ½ hour, 127.0; 1 hour, 129.0; 2 hours, 113; 3 hours, 90.0; 4 hours, 26.8; 5 hours, 30 mg. per cent. Between the fourth and fifth hour the patient became quite listless and began to perspire.

On February 20, desoxycorticosterone was increased to 2.5 mg. daily. On March 9, seventeen days later, the blood chemistry had returned almost to normal. The serum concentration of chloride was 110.5, of potassium was 5.9 and of sodium was 141.8 milliequivalents per liter.

Following the increased dose of "DOCA" the child became her usual self, the appe-

tite increased and she regained her strength. There was no longer the desire for extra table salt, although the appetite had returned to normal.

On March 18, 1946 Dr. Peter Heinbecker implanted four 125 mg. desoxycorticosterone acetate pellets. This has been a great help, since the daily injections are no longer necessary. The child has been well controlled with the absorption of desoxycorticosterone afforded by the pellets.

SUMMARY

A case of Addison's disease in a female infant, aged six months, is reported. The clinical course, with rapid dehydration following the discontinuance of parenteral fluids, a characteristic blood chemical change, the gradually increasing skin pigmentation, and the prompt response to the administration of desoxycorticosterone acetate substantiates this diagnosis.

Hypoglycemia of severe degree, with fasting blood glucose levels of from 20 to 26 mg. per cent was a prominent feature whenever food intake was interrupted by lapses into adrenal cortical failure. When food intake was maintained at regular intervals in response to adequate amounts of desoxycorticosterone acetate, the blood glucose levels tended to remain within normal limits. Beef adrenal cortex had little effect upon the blood glucose level, but definite elevation of blood glucose followed injection of pork adrenal cortex extract.

The failure to find an adrenal tumor, the absence of abnormal sex manifestations, and the known exposure to active tuberculosis, plus a markedly positive tuberculin skin test suggest that tuberculosis is the etiological agent responsible for hypofunction of the adrenal cortex in this child.

The patient's course has been followed for over two years. She has remained active, well nourished and maintained normal mental and physical development, while receiving 2 to 2.5 mg. of desoxycorticosterone acetate daily. On March 18, four 125 mg. pellets of desoxycorticosterone acetate were implanted into the interscapular region. The patient has continued to do well and is much happier since the daily injections have been eliminated.

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METABOLIC STUDIES IN CHILDREN FED MILK FROM COWS RECEIVING SYNTHETIC THYROPROTEIN

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REINEKE and Turner (16) showed that the feeding of iodinated milk proteins to lactating cows and goats for short periods increased milk production with corresponding increases in the yield of butterfat. This confirmed the earlier observations of Graham (10), Jack and Bechdel (12), Folley and White (9), Herman *et al.* (11) and Ralston and his associates (13) who stimulated milk production in cows by the administration of desiccated thyroid or thyroxine.

From an economic standpoint, these findings may prove to be of practical significance. According to some workers, however, the augmentation of milk and butterfat output by these methods may not be without some disadvantages. Van Landingham, Henderson and Weakley (29) and Seath, Branton and Groth (26) noted increases in pulse rate, body temperature and respiratory rate and a decrease in body weight of cows fed synthetic thyroprotein. On the other hand, Reineke (15) failed to observe these effects in 27 cows of three different breeds fed 1.5 to 2.5 grams of thyroprotein per 100 pounds of body weight over a period of three months. Milk production was increased significantly, nevertheless, in 23 of the 27 cows.

The present investigation was undertaken to determine whether children ingesting milk from cows fed thyroprotein would manifest any harmful side-effects. The studies included observations on height, weight, pulse, body temperature, basal metabolic rate, respiratory quotient, partial pressure of carbon dioxide in the expired air, plasma cholesterol and plasma protein-bound iodine (hormonal iodine).

EXPERIMENTAL PROCEDURE

Twenty-one children were studied. Nine (six males and three females) between the ages of six and thirteen years served as controls while twelve (eight males and four females), age nine to fourteen years, comprised the experimental subjects. Older children rather than infants were chosen so as to make more complete metabolic studies possible. All were healthy children maintained on an average American diet at a home for children

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in Brooklyn, New York. The milk feedings were carefully supervised by responsible individuals attached to the home. At stated intervals, the children were brought by automobile to this institution for the studies herein reported.

The observations were made on both groups at three intervals: the initial series at the beginning of the experiment, a second series from 37 to 44 days after the milk feedings were started, and the third series after the milk was fed for from 108 to 116 days.

The basal metabolic rate was determined by the gasometer method as modified by Bailey (1) employing the technics outlined in a paper by Bruger and Rosenkrantz (4). The respiratory quotient and partial pressure of carbon dioxide in the expired air were determined simultaneously by gas analysis. Boyer and Bailey (2) demonstrated that the partial pressure of carbon dioxide in the expired air is constant in normal subjects within the range of from 18.0 mm. to 22.5 mm. of mercury; values are expressed as per cent of average normal where 20 mm. of mercury equals 100 per cent. The plasma was analyzed for cholesterol by the Sackett modification of Bloor's method (25), and for hormonal iodine (protein-bound iodine) by the method of Trevorrow (27) as amplified by Bruger and Member (5). The total iodine content of the control and experimental milks was determined by the procedure of Trevorrow and Fashena (28) and Fashena and Trevorrow (7).

The milk was produced by cows in the dairy herds of the State of New Jersey Agricultural Experiment Station, Rutgers University, New Brunswick, New Jersey. The cows were handled under ordinary herd conditions. Five control and six experimental animals were employed. The cows in the experimental group received 15 grams of synthetic thyroprotein daily incorporated in the grain ration. Each cow in the experimental group showed evidence of response to the fed thyroprotein before being placed in this group.

The milk saved from the night and morning milkings was combined for each group and pasteurized (145° F. for 30 minutes) in a 20-quart milk can. Efficiency of pasteurization was checked by the phosphatase test. Bacteria counts were made according to the standard plate method. The milks (control and experimental) were sent to the home on the day after pasteurization. The control milk was labelled with a red tag and the experimental milk with a yellow tag. The home supervisors were unaware of the identity of each.

The children in the control group were fed 720 cc. (24 ounces) of milk from the control cows daily. This milk contained 3 micrograms of iodine per 100 cc. The children in the experimental group received the same

quantity of milk from cows receiving synthetic thyroprotein. This milk contained 80 micrograms of iodine per 100 cc.

RESULTS

In order to conserve space, the detailed findings in the 21 children during the several phases of the investigation are omitted. Table 1 indicates the range and average change from the initial studies in weight, height, basal metabolic rate, plasma protein-bound iodine, plasma cholesterol, basal pulse rate, respiratory quotient and partial pressure of carbon dioxide in the expired air in the nine control children and in the 12 children ingesting milk from cows fed synthetic thyroprotein. This protocol shows that children ingesting milk from cows fed thyroprotein (a) increased in weight and height to the same degree as those fed milk from control cows, (b) manifested no elevation in the basal metabolic rate, (c) failed to show significant variations in plasma protein-bound iodine and plasma cholesterol, and (d) demonstrated no alteration in basal pulse rate, respiratory quotient and partial pressure of carbon dioxide in the expired air.

TABLE 1. Average change from initial values in weight, height, basal metabolic rate, protein-bound plasma iodine, plasma cholesterol, basal pulse rate, respiratory quotient and partial pressure of carbon dioxide in the expired air in nine control children and in twelve children ingesting milk from cows fed synthetic thyroprotein.

	37–44 days				108–116 days			
	Control		Experimental		Control		Experimental	
	Range	Average	Range	Average	Range	Average	Range	Average
Weight (lb.)	− 1 to + 2	+ 1	− 1 to + 3	+1	0 to + 5	+ 3	+ 1 to + 9	+4
Height (cm.)	+ 1 to + 1.5	+1.2	0 to + 2	+1	+ 1 to + 3.5	+ 2.1	+ 1 to + 3.5	+2.1
Basal metabolic rate (per cent of normal)	− 6 to +10	−1	− 7 to + 6	−1	−15 to + 4	− 6	−12 to + 3	−3
Plasma protein-bound iodine (μg. per cent)	− 0.8 to + 8.6	+3.8	− 4.2 to + 8.1	+2.4	− 0.8 to + 6.3	+ 2.9	− 1.3 to + 6.8	+2.5
Plasma cholesterol (mg. per cent)	−49 to +17	−15	−27 to +58	+8	−50 to +28	− 5	−46 to +39	−2
Basal pulse rate (per minute)	−12 to +10	+2	0 to +12	+4	−20 to 0	−12	−14 to + 4	−5
Respiratory quotient	+ 0.01 to + 0.10	+0.04	− 0.04 to + 0.05	+0.01	− 0.05 to + 0.07	+ 0.02	− 0.06 to + 0.07	−0.01
Partial pressure of CO_2 (per cent of normal)	−15 to + 5	−1	− 8 to + 5	0	− 4 to +16	+ 2	− 6 to + 8	0

DISCUSSION

Since Reineke (14), Reineke and Turner (17) and Reineke, Williamson and Turner (22, 23) showed that by assay, synthetic thyroprotein is as

active or more effective than U. S. P. thyroid and that the active principle is identical with thyroxine [Reineke and Turner (18–20)], it would appear on first analysis that subjects ingesting milk from cows fed synthetic thyroprotein might show an increase in basal metabolic rate and pulse rate accompanied by some weight loss. As described above, this was not observed.

Boyer and Bailey (3) demonstrated that partial pressure of carbon dioxide in expired air may be utilized to evaluate relative cardiac and circulatory efficiency. They pointed out that in patients with hyperthyroidism as the pulse accelerates with progressive elevation of the basal metabolic rate, a slight but definite downward trend in carbon dioxide partial pressure occurs. In this study no increase in pulse rate was noted so that it is not remarkable that the partial pressure of carbon dioxide in the expired air of the subjects remained unchanged.

Robertson (24) has shown that the feeding of one quart of milk daily from cows fed iodinated protein to 27 normal healthy women (age-range of from 19 to 33 years) for a period of four weeks produced no increase in the basal metabolic rate, pulse rate or blood pressure. Reineke and Turner (21) demonstrated that the feeding of milk from thyroprotein stimulated cows failed to modify the basal metabolic rate in guinea pigs, goats and two human subjects. Nevertheless, these workers showed that the direct administration of either thyroxine or synthetic thyroprotein to animals and humans resulted in a significant rise in basal heat production. They concluded that the mammary gland of the cow does not permit the passage of the thyroid hormone into the milk. The present studies appear to substantiate this conclusion.

High concentrations of inorganic iodine (metabolically inert) probably account for the increased content of total iodine in the experimental milk (80 micrograms per cent) as compared to the control milk (3 micrograms per cent). Iodine in this form readily permeates other glands of the organism [Flexner, Bruger and Member (8), Bruger and Member (6)]. The assay of the milk for protein-bound (hormonal) iodine was attempted but the results were unreliable because of the relatively high fat content of the milk.

CONCLUSIONS

1. The ingestion by children over a period of from 108 to 116 days of milk from cows fed synthetic thyroprotein failed to alter significantly the height, weight, basal metabolic rate, protein-bound plasma iodine, plasma cholesterol, basal pulse rate, body temperature, respiratory quotient or the partial pressure of carbon dioxide in the expired air.

2. In view of the high total iodine content of such experimental milk, theoretical considerations are presented to indicate that hormonal iodine probably failed to pass through the mammary gland of the cow.

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THERAPEUTIC USE OF TESTOSTERONE IN AQUEOUS SUSPENSION

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BOTH the male and female sex hormones are customarily dissolved in vegetable oil for the purpose of parenteral therapy. These preparations are widely used and are quite satisfactory. There is, however, a significant incidence of a local allergic or irritating action at the site of injection due to the oil. These local reactions are not infrequent, and depend upon the type of vegetable oil used as a vehicle. Those commonly used are derived from sesame, peanut and corn, and the incidence of reactions due to some of these oils may amount to 20 per cent. Sesame oil seems to be the least allergenic. The local induration, itching, bleb formation and swelling of the neighboring tissues are often slight for the first one or two injections, but they become increasingly severe and may cause significant disability and pain for relatively long periods of time. Occasionally a patient will respond to the first injection with a severe reaction. We have demonstrated that the suspension of estrone crystals in water is effective for estrogen therapy as well as giving freedom from possible allergic reactions (1) to the oils.

This suspension of estrogen, now available commercially, has proven satisfactory not only from this standpoint, but also because of its increased effectiveness over estrone dissolved in oil. This increased effectiveness is probably due to a slower rate of absorption of the estrone crystals from the site of injection, since, following the rapid absorption of the aqueous vehicle, the crystals of estrone behave like small implants which are more slowly absorbed from the tissues than the oil solution. Similar results are being reported elsewhere with aqueous suspensions of diethylstilbestrol (2). We have therefore extended our experiments with aqueous suspensions to the commonly used androgen, testosterone.

Testosterone in oil is relatively inactive for therapeutic purposes because of its rapidity of absorption and destruction when it is administered by injection. For this reason it has been combined with propionic acid, and this increases its effectiveness about fourfold, due to the delay in absorption and lessened destruction (3). Following our experiments with the aqueous estrone and diethylstilbestrol suspensions, we sought to determine whether a similar preparation of testosterone would be sufficiently effective to make it a worthwhile therapeutic agent as well as to offer the advantage of being free from the induction of the local reactions.

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The commonly accepted method of testing the androgenic effect of a compound is to administer the preparation to castrate or eunuchoid males and to determine the dosage required to maintain their masculinity. This method is quite accurate but also cumbersome and laborious, and suitable patients are not readily obtained. We have, however, already demonstrated that testosterone propionate is effective in producing a relief of premenstrual tension, and women with this condition are frequently encountered in private practice (4). We considered the possibility of determining the action of the aqueous testosterone preparation[1] in these women in order to tc compare its therapeutic effect with that of testosterone propionate. In such experiments involving the subjective relief of symptoms, it is advisable to use controlled injections at different dosage levels as well as placebo injections in order to control psychotherapeutic and other non-specific factors. A similar assay method was reported by us in determining the potency of estrogens using menopausal women and evaluating their subjective relief (5, 6).

In the present experiment, groups of women with premenstrual distress of a significant degree, such as increased nervousness, irritability, headaches, depression, emotional instability, *etc.*, were administered the following preparations on about the seventh day before the expected day of onset of the menses: 20 mg. of testosterone crystals suspended in water; 25 mg. and 10 mg. of testosterone propionate in oil; and a placebo. In the following tables the results with these injections are indicated; the plus signs signifying the relief of these patients after the administration of the preparations; three plus signifying complete relief; two plus, moderate relief; one plus, slight relief; and zero, no relief. Without doubt a number of non-specific factors influence the evaluation of the patient's response to the medication. These factors include the general state of health, the power of suggestion in the doctor-patient relationship, and the occasional absence of premenstrual tension which occurs for some reason, possibly due to an anovulatory cycle. For these reasons it is essential to use relatively large numbers of individuals and to administer several dosage levels of medication, which minimize and cancel out these factors. By this experimental method, a reliable conclusion can be drawn as to the therapeutic effectiveness of the agents used.

It can be noted from the tables (page 573), that the majority of women responded with successful relief of their symptoms after the administrations of both 10 mg. and 25 mg. of testosterone propionate in oil, the larger dose being considerably more effective in producing complete relief, but

[1] Testosterone crystals in aqueous suspension were prepared and furnished by Abbott Laboratories, North Chicago, Illinois.

EFFECT OF MEDICATION ON RELIEF OF PREMENSTRUAL DISTRESS

25 mg. testosterone propionate in oil			
No. of patients	No. of treatments	Degree of relief	
60	92	60	+++
		24	++
		4	+
		4	0
10 mg. testosterone propionate in oil			
No. of patients	No. of treatments	Degree of relief	
58	98	44	+++
		36	++
		10	+
		8	0
20 mg. testosterone in aqueous suspension			
No. of patients	No. of treatments	Degree of relief	
56	84	42	+++
		28	++
		9	+
		5	0
Placebo injections			
No. of patients	No. of treatments	Degree of relief	
20	30	3	+++
		5	++
		6	+
		16	0

the 10 mg. dose being quite satisfactory in most cases. It can be also noted that 20 mg. of testosterone crystals in aqueous suspension induces relief from the premenstrual symptoms in the majority of cases to a satisfactory degree.

Our results indicate that 20 mg. of testosterone in aqueous suspension is at least as effective in controlling the symptoms of premenstrual distress as 10 mg. of testosterone propionate in oil. Since testosterone in oil is about one fourth to one fifth as potent as testosterone propionate in oil, it would appear that the aqueous suspension of testosterone is at least twice as active as the same material dissolved in oil, and this increase in activity is probably the result of its slower absorption into the blood stream when injected in the form of an aqueous suspension, much the same as with estrone

and diethylstilbestrol. Testosterone in aqueous suspension is sufficiently potent to make it a worthwhile therapeutic agent in the treatment of premenstrual distress. In view of the fact that this preparation is free from the local allergic reactions, there is a definite need for such a preparation in the endocrine armamentarium. It still remains to be demonstrated that this preparation is sufficiently effective in treating other conditions where androgen therapy is indicated, although it can be mentioned that we already have data which indicates that it is useful in treating functional cryptorchidism in boys. That it provides relief for the condition of premenstrual distress is in itself reason for its usefulness, since there are such large numbers of women demonstrating this condition, who are gratified to obtain relief from it.

SUMMARY

1. A preparation of testosterone crystals suspended in water has sufficient therapeutic activity to make it a therapeutically practical product.

2. Such a preparation is at least half as potent as testosterone propionate in oil.

3. Through the use of this preparation, one avoids inducing local allergic reactions to the oil vehicles in which androgens are presently dissolved.

4. 20 mg. of testosterone propionate in aqueous suspension or 10 mg. of testosterone propionate in oil are highly effective in controlling premenstrual distress.

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HEREDITARY EXOPHTHALMIC GOITRE— REPORT OF ELEVEN CASES IN ONE FAMILY[1]

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HEREDITARY exophthalmic goitre is frequently encountered, and, yet, the presence of the disease in more than three members of one family is uncommon. Romberg (55) was the first to record the familial occurrence of exophthalmic goitre when in 1851 he reported its presence in twin sisters, twenty years of age. Withusen (71), eight years later, was the first to suggest a hereditary factor in this disease but he was unable to substantiate his impression. In 1871 Solbrig (60) described the disease in a woman and in her eight year old son. Four authors (44, 54, 59, 72) have reported families each with six members afflicted with the disease.

The family we present has eleven members with exophthalmic goitre. This family was described by Morrison (44) in 1928, at which time only six members had developed the disease. In this communication a hereditary study of exophthalmic goitre and other diseases occurring in this family is presented. Complete case histories were obtained on those members with evidence of thyroid diseases.

REVIEW OF THE LITERATURE

Of 157 reports, only 70 were considered suitable for discussion, due to the many inadequate clinical descriptions, especially in the earlier articles.

Oesterreicher (48) in 1884 reported a family in which there were eleven cases of exophthalmic goitre, but his case reports are too brief to warrant more than suggestive diagnoses in five or six cases. Lermoyez and Souques (37) presented a family with seven cases of exophthalmic goitre in three generations, but gave only four case histories. Euziere, Viallefont, Castagné, and Lafon (24) reported six instances of Basedow's Disease in four generations of one family, but none with exophthalmos. Schachter (59) reported on nine cases of exophthalmic goitre in three generations, but only six case reports are convincing.

The presence of exophthalmic goitre in five members of a family was mentioned twice, by Riebold (54) and Lenz (36). Five writers (6, 9, 14,

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36, 69) presented families with four cases in each. Twelve writers (13, 22, 26, 29, 30, 45, 50, 51, 54, 57, 63, 65) presented families with three cases in each. There are twenty-six reports of exophthalmic goitre in two family members. Over one-third of these reports deal with the presence of exophthalmic goitre in a mother and a daughter (1, 4, 21, 27, 41, 43, 49, 64, 66, 68); another third with its presence in sisters (23, 44, 47, 55, 61, 63, 67), three pairs of female twins being mentioned (47, 55, 63). The remaining third (8, 12, 25, 31, 33, 35, 43, 52, 58, 60, 63) report other family combinations. The only other twins with exophthalmic goitre mentioned in the literature were males, described by Fife (25) in 1940. The only convincing report of a child born with exophthalmic goitre was that of White (68). The baby was premature and born to a mother who had developed this disease in her fifth month of pregnancy. The child died soon after birth and an autopsy confirmed the diagnosis.

Reports on the familial incidence of exophthalmic goitre vary considerably. Atkinson (3) reported a history of "thyroid disease" in 18.8 per cent of a series of 208 patients with juvenile exophthalmic goitre. In a series of 124 cases of juvenile exophthalmic goitre, Dinsmore (20) stated that 11.3 per cent gave a family history of exophthalmic goitre. Curtin (17, 18), by inquiries among physicians about the familial incidence of exophthalmic goitre, was able to accumulate 137 cases in 52 families, suggesting that its actual incidence in families is higher than generally assumed. Most of his cases were, however, not well substantiated. Murray (46) was able to obtain a family history of exophthalmic goitre in 4 per cent of 120 cases. Moolten and Bruger (43) reviewed the literature on juvenile exophthalmic goitre and reported on 93 cases of the disease in 66 families; many of the articles they referred to gave unconvincing reports. In studying children, Kerley (34) said,

> In 24 of 104 cases (23 per cent) we have proof of thyroid gland impairment in the mother or immediate family.

Rankin and Priestly (53) stated,

> In a larger group (22 per cent) there was a positive family history of goitre, usually of the exophthalmic type, and frequently more than one other member of the family had been affected.

They do not state how large their group was. Black and Webster (5), Joffroy (32), Rose, Rose and Pendergrass (56) all report high incidences in small series.

METHOD OF STUDY

In December 1944, a patient (*Case 11*) with essential hypertension entered the Massachusetts General Hospital for a bilateral lumbodorsal

sympathectomy. She stated that several members of her family had "toxic goitre." She presented no evidence of thyroid disease. With her aid a family tree was worked out which included over 125 of her relatives. A brother (*Case 9*) was consulted and this chart was compared with a genealogical study he had made of the same family in 1916. Subsequently many of the members of the family were interviewed, and the chart was completed. In all, out of 143 blood relatives in the family, 23 of whom were dead, 32 were consulted—4 by mail, 17 by telephone, and 11 were seen personally. These interviews included each small family group. With regard to every member of the family, the following data were obtained: age, sex, cause of death if dead, histories of thyroid disease or symptoms referable to the thyroid gland, arthritis, rheumatic fever, diabetes mellitus, tuberculosis, nervous disease, miscarriages, stillbirths and migraine headaches. Sixty-five persons married into the family. The above data were also secured on them.

The following criteria were employed for the diagnosis of exophthalmic goitre. They were: characteristic symptomatology (*i.e.* sweating, tremor, weight loss, cardiac palpitation, diarrhea, myasthenia and nervousness), exophthalmos, an enlarged thyroid gland, a convincing pathological report and an elevated basal metabolic rate. Hospital and private records of 16 members of the family who had presented symptoms suggestive of thyroid disease were studied, as a result of which three were eliminated. One thyroid history was obtained by personal interview.

FINDINGS

A white Jewish family of Hungarian descent with 208 members in 5 generations was studied. Of these, 143 were blood relatives and 65 had married into the family. Eleven (7.7 per cent) proved cases of exophthalmic goitre, one case of non-toxic thyroid adenoma, and one case of primary hypothyroidism were found. One patient with exophthalmic goitre developed Addison's Disease and another developed diabetes mellitus.

Of the members with exophthalmic goitre, eight were females and three were males. The disease was seen in two consecutive generations, II and III (see Fig. 1). The distribution of the cases of exophthalmic goitre is striking. In Generation II, three sisters out of six siblings had the disease. One of these (*Case 1*) had 12 children, six of whom had exophthalmic goitre. Another case occurred in a daughter of one of these sisters (*Case 3*). Finally, one (*Case 14*) was observed in the daughter of a normal sibling in Generation II.

Case 1.—C.O. (Massachusetts General Hospital, *#245,171, #251,430*) Exophthalmic goitre

This patient, a housewife, was first seen at the Massachusetts General Hospital in

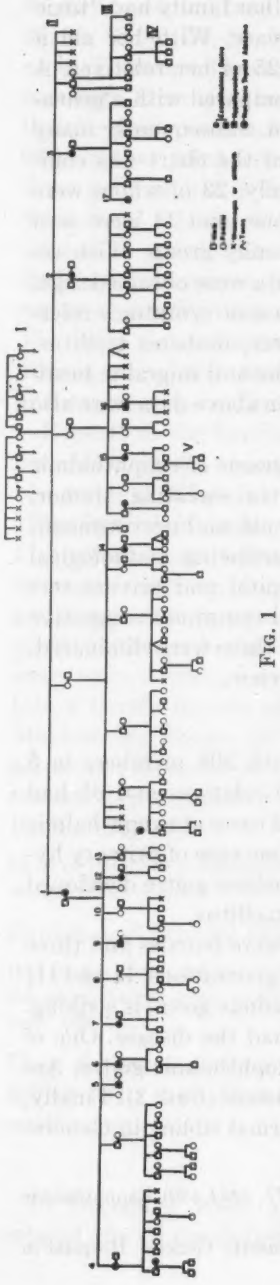

FIG. 1

1922 at the age of 61. Her presenting complaints were weakness, nausea, dizzy spells, nervousness and a loss of 25 pounds in weight. Her skin was moist; there was a fine tremor of the extremities; the blood pressure was 200/110 mm. Hg.; the pulse rate was 112 and the heart was enlarged. Basal metabolic rate levels on two occasions were plus 53 per cent and plus 52 per cent. Despite x-ray treatments over the thyroid gland she developed bilateral exophthalmos and her basal metabolic rate remained above 41 per cent. A right hemithyroidectomy was performed in 1923. The specimen on histological examination showed hyperplasia and round cell infiltration. There was no recurrence of thyroid symptoms, and she died 10 years later of a cerebro-vascular accident.

In view of the fact that this patient had six children with exophthalmic goitre, her husband's family was studied to determine if there were any members there with thyroid disease. No cases were found in five generations. It is interesting to note that five other children developed rheumatoid arthritis (*Cases 8* and *11*), rheumatic heart disease (*Case 13*) an anxiety neurosis with cyclic depressions (*Case 10*) and essential hypertension (*Case 11*) respectively.

Case 2.—R.K.G. (Massachusetts General Hospital, *#1457BM*) Exophthalmic goitre

This housewife was well until February, 1930, at which time she underwent severe psychic trauma. One month later at the age of 60 she was admitted to the Massachusetts General Hospital complaining of nervousness, palpitation, dyspnea and precordial pain on exertion, diarrhea and a weight loss despite an increased appetite. Physical examination revealed a tremor, bilateral exophthalmos, and a large firm goitre over which a bruit was heard. The pulse rate was 120 a minute and the blood pressure was 146/76 mm. Hg. Her pre-treatment basal metabolic rate was plus 63 per cent. It fell to plus 32 per cent when iodine was administered. A subtotal thyroidectomy was performed. Histological section revealed moderate hyperplasia with focal collections of lymphocytic cells in the stroma. The patient was discharged improved, is now 75 years old, and has had no recurrence of her thyroid symptoms.

Case 3.—E.W. (The history was obtained from the patient's husband and a daughter) Exophthalmic goitre

In 1908, at the age of 29, this housewife "suddenly became sick." Her neck became enlarged so that she had difficulty in swallowing and at times got short of breath. Both eyes gradually "stuck out of her head" and she became very nervous complaining of palpitation, cramps in the legs and headaches. In the same year Dr. Maurice

Richardson operated on her thyroid gland at the New England Deaconess Hospital. (The old hospital records have since been destroyed.) Following the operation the patient was free of her symptoms except for persistent exophthalmos. She died at the age of 42 of a hemorrhage following an operation for a uterine tumor.

Case 4.—R.C. (Massachusetts General Hospital, *#151,301, #162,188, #179,615, #193,589, #253,974*; Lahey Clinic) Exophthalmic Goitre

This housewife was first seen at the age of 26 during her second pregnancy. She complained of palpitation, headaches, weakness, dysphagia, insomnia, urinary frequency and increased sweating. She was admitted to the Massachusetts General Hospital one year later, in 1907, at which time she had a tremor of the hands, marked bilateral exophthal-

FIG. 2

mos, an enlarged pulsating thyroid gland with a palpable thrill and a systolic bruit. She was treated with "thyroidectomized goat serum and bromides of quinine." Two years later she was readmitted with the same symptoms. A right hemithyroidectomy was performed by Dr. Maurice Richardson. Microscopically the specimen showed marked hyperplasia with papillary infoldings into many of the follicles (see Fig. 2). Following her third pregnancy the above symptoms returned, and in 1911 a left hemithyroidectomy was performed. She remained well until 1915 when she developed an exacerbation of her previous symptoms during her fourth pregnancy. She had temporary remission with x-ray treatments but in 1923 was readmitted to the Massachusetts General Hospital with a basal metabolic rate of plus 27 per cent. The remaining isthmus and pyramidal lobe were removed. The pathological report was the same as above. During the next five years she developed a "lemon-sized mass" in the thyroid area and her symptoms recurred despite iodine therapy. In 1928 she was seen at the Lahey Clinic

where "multiple remnants were removed" from both sides of the thyroid area. Microscopic section revealed "primary hyperplasia with early irregular involution and a Grade 2 strumitis." She has since had evidence of mild hypothyroidism with basal metabolic rates varying between minus 21 per cent and minus 25 per cent. At present she is 65 years old, and her exophthalmos is still present and marked.

This patient presented unusual persistence of exophthalmic goitre despite four operations. Three of her exacerbations were associated with pregnancy.

Case 5.—S.O. (St. Vincent's Hospital, Los Angeles, California) Exophthalmic goitre

This man, a grocer, was well until the age of 47 at which time he received a blow on the head. Shortly after this incident he began to feel restless and apprehensive; he perspired readily, exhibited a marked tremor of the hands, became easily fatigued and developed a tachycardia with palpitation. He lost 30 pounds in six months despite an increased appetite. He had temporary relief when treated with Lugol's solution; however, enlargement of the thyroid gland and slight bilateral exophthalmos gradually appeared. A subtotal thyroidectomy was performed at the St. Vincent's Hospital in June, 1935. Microscopic examination revealed "hyperplasia of thyroid, very marked." Since the operation he has been in good health.

Case 6.—E.O. (Lahey Clinic) Exophthalmic goitre

This patient, a constable, was first seen at the Lahey Clinic in 1927 at the age of 39. He had developed a tremor of his hands and feet on exertion, sweating, nervousness, bilateral exophthalmos and an increased appetite with a weight loss of 20 pounds. A basal metabolic rate was plus 50 per cent. On admission his pulse rate was 108 and his blood pressure was 138/70 mm.Hg. Because of the severity of his symptoms and his lack of response to pre-operative rest and medication, a subtotal thyroidectomy was performed in two stages. The pathological report revealed primary parenchymatous hyperplasia with early involution. His exophthalmos has remained unchanged, but he has had no recurrence of symptoms referable to his thyroid gland.

Case 7.—J.L. (Massachusetts General Hospital *#234,552, #236,650, #352,713, #406,293*) Exophthalmic goitre, Addison's disease

In 1920 this housewife, aged 30, was admitted to the Massachusetts General Hospital. She complained of frontal headaches, nervousness, tremor of the hands, and a 25 pound weight loss despite an increased appetite. Physical examination revealed a bilateral exophthalmos and an enlarged thyroid gland. The heart was markedly enlarged and the blood pressure was 170/95 mm. Hg. The basal metabolic rate was plus 55 per cent. Following x-ray treatments over the thyroid gland the basal metabolic rate fell to plus 16 per cent. Three months after discharge she was readmitted complaining of increased sensitivity to cold, and constipation. Menorrhagia had replaced a previously scanty flow. Her eyelids, lips and face were puffy and she had gained 22 pounds. The blood pressure was 150/85 mm. Hg. She was treated with thyroid but these symptoms persisted until 1934, when she developed brown pigmentation of the skin and buccal mucosa. In February 1936 her pulse rate was 48 per min. and her basal metabolic rate was minus 8 per cent. In March, 1936, thyroid was again prescribed. One month later she was readmitted following two attacks of syncope. She had lost 17 pounds in two months and had not menstruated in three months. On physical examination she was lethargic, obese, and retched easily. The skin was dry, coarse, and brown; small brown spots were seen on the buccal mucosa. The pulse rate was 62 per min. and the blood pressure was 80/60 mm. Hg.

Laboratory studies revealed a blood sodium of 126.6mE per liter, chloride of 90.2mE per liter, non-protein nitrogen of 73 and 59 mg. per 100 cc., hematocrit of 43.7 per cent,

serum protein of 6.7 grams per 100 cc., blood sugar of 112 mg. per 100 cc., and a serum bicarbonate of 53.5 volumes per cent. Electrocardiographic examination showed left axis deviation, low voltage, and myocardial changes. During her hospital stay she developed an acute toxic psychosis. She was treated with intravenous glucose, saline, and adrenal cortical extract in the form of *Cortin* and *Eschatin*. Two weeks later the patient entered the emergency ward in a "mixed crisis." She had not taken her medications. She was discharged after treatment and one week later had an exacerbation of the psychosis. She died suddenly, four days later, at the age of 46. Permission for autopsy was denied (40).

In the hospital record Dr. S. Hertz stated, "It is well recognized that Thyroid medication may cause a crisis in Addison's disease and that may well have been the case here." Williams (70) believes that hypothyroidism may lead to exhaustion atrophy of the adrenal cortex and that with such a picture thyroid therapy might well initiate adrenal insufficiency.

Case 8.—H.G. (Personal Interview) Rheumatoid Arthritis

Case 9.—H.O. (Beth Israel Hospital, Boston, *#76,881*) Exophthalmic goitre

This man, a certified public accountant, was in essentially good health until the age of 49. In 1944 he was admitted to the Beth Israel Hospital complaining of increasing fatigue, irritability, palpitation, insomnia, decreased appetite and a loss of weight. Physical examination revealed a normal heart with occasional extrasystoles, and tachycardia. The blood pressure was 145/72 mm. Hg. He had a rapid tremor of the hands and perspired freely. The basal metabolic rate was plus 32 per cent, plus 41 per cent and plus 51 per cent on three occasions. After a course of iodine therapy the basal metabolic rate fell to minus 1 per cent but bilateral exophthalmos and an enlarged thyroid gland were first noted. The basal metabolic rate again rose, and in December, 1944, he consulted Dr. James H. Means and Dr. Earle M. Chapman. He was treated with radio-active iodine, receiving 50 millicuries in February, 1945, and 40 millicuries in April, 1945. One month later his basal metabolic rate had fallen from plus 55 per cent to plus 19 per cent and he had gained 18 pounds in weight.

Case 10.—G.L. (Peter Bent Brigham Hospital, *#51,440*) Anxiety neurosis with cyclic depressions

Case 11.—B.O. (Massachusetts General Hospital *#470,618*) Essential hypertension

Case 12.—M.C. (Elliot Hospital, Manchester, N.H.) Exophthalmic goitre

This housewife, in 1938 at the age of 36, experienced spells of diplopia coming on each morning. This was relieved when her glasses were changed but her eyes became very prominent. She developed nervousness, weakness, dysphagia, tachycardia and weight loss. When admitted to the Elliot Hospital five months later she had bilateral exophthalmos, a diffusely enlarged thyroid gland over which a bruit was heard, and a tremor of the hands. An initial basal metabolic rate was plus 73 per cent but following iodine treatment it fell to plus 25 per cent. A subtotal thyroidectomy was subsequently performed. Microscopic sections revealed parenchymatous hyperplasia with some areas of lymphoid infiltration. She is now 43 years old and has had no recurrence of her thyroid symptoms.

Case 13.—E.O. (Beth Israel Hospital, Boston, *#33,448*) Rheumatic Heart Disease with mitral and aortic stenosis

Case 14.—M.B. (Massachusetts General Hospital, *#258,372*, Lahey Clinic) Exophthalmic goitre, diabetes mellitus

This patient, a housewife, was well until the age of 27. In 1923, three months following the delivery of her first baby, she developed ease of fatigue, dyspnea, palpitation on

exertion, increased sweating, intolerance to heat, an increased appetite, and a 20 pound weight loss. On admission to the Massachusetts General Hospital her thyroid gland was enlarged, firm, and presented a thrill and bruit. A fine tremor of the hands, bilateral exophthalmos and tachycardia were present. An initial basal metabolic rate was plus 57 per cent. Following treatment with Lugol's solution and x-ray over the thyroid area, her basal metabolic rate fell to minus 2 per cent, and her symptoms gradully disappeared. Four years later following the death of her mother, all of her symptoms returned and her basal metabolic rate rose to plus 45 per cent. These symptoms had persisted two years when she was seen at the Lahey Clinic. At this time a basal metabolic rate was again plus 45 per cent, the blood pressure 160/70 mm. Hg. and the pulse rate was 110 per min. A subtotal thyroidectomy was performed. The pathological report was primary hyperplasia with late involution. In the first few days postoperatively she developed persistent glycosuria, necessitating a diabetic dietary regimen, but required no insulin. She continues to take Lugol's solution, and is now free from symptoms referable to the thyroid gland.

This is only member of the family found to have diabetes mellitus.

Case 15.—R.W.G. (Lahey Clinic) Thyroid adenoma

This housewife noticed a swelling in her neck at the age of 27. It gradually increased in size over the next 13 years. In 1935 she visited the Lahey Clinic and at this time the thyroid gland was described as being plum-sized. Basal metabolic rates were minus 7 per cent and minus 10 per cent and she had no symptoms suggesting thyroid dysfunction. A thyroid adenoma was excised. The microscopic diagnosis was "multiple colloid adenomatous goitre." The patient is now 50 years old and is free from all evidence of thyroid disease.

Case 16.—M.W. (Case of Dr. Samuel L. Gargill) Hypothyroidism

This man, a salesman, age 40, well until 1942, started to gain weight and became drowsy. Eight months later he consulted Dr. Samuel Gargill complaining of ease of fatigue, extreme sensitivity to cold, marked constipation, a loss of appetite and weight loss. On physical examination his face was full and puffy; his skin was cool, dry and thickened. His basal metabolic rate was minus 33 per cent, the serum cholesterol was 411 mgm. per 100 cc., the hemoglobin was 68 per cent and the erythrocyte count was 3.80 million per cu. mm. Following treatment with thyroid his face became less puffy, he tired less readily and his tolerance to cold increased. His anemia was corrected, the serum cholesterol approached normal and the basal metabolic rate became normal. In January, 1944, the patient complained of impotency. His wife had had three pregnancies ending in early miscarriages. A spermatozoa count at this time was from 15 to 30 million per c.c. with from 60 to 70 per cent abnormal forms. The patient has continued to take his thyroid and his hypothyroidism is now well controlled.

Case 17.—A.W. (Ross-Loos Medical Group, Los Angeles, California) Exophthalmic goitre

This unmarried secretary was well until 1941, when at the age of 43 she consulted the Ross-Loos Medical Group complaining of a rapid heart, tremor, and loss of 10 pounds in weight. She had slight bilateral exophthalmos, and her basal metabolic rate was plus 22 per cent. A diagnosis of exophthalmic goitre was made, and treatment with Lugol's solution instituted. One year later she returned with the same symptoms. Two basal metabolic rates were plus 10 per cent and plus 15 per cent. Following a thyroidectomy performed by Dr. Donald Ross, her basal metabolic rate returned to normal, and her symptoms disappeared. Histological examination of the thyroid gland revealed involution. This was ascribed to the iodine therapy. She has returned to work and has remained free from thyroid symptoms.

SUMMARY OF CASE-MATERIAL

The ages of onset varied between 26 and 61 years. The mean age of onset was 41 years. No correlation between sex and age of onset could be established. Precipitating factors could be determined in only four cases. In one case the onset was during pregnancy; in one case the onset was preceded by emotional trauma; in another, the onset was within three months postpartum and a fourth developed symptoms of exophthalmic goitre following a blow on the head.

Definite evidence of exophthalmos was present in 100 per cent of the cases. There was evidence of enlargement of the thyroid gland in eight cases. Tachycardia, tremor and weight loss were present in ten cases and other symptoms were present in varying degrees.

Nine of the eleven patients were treated surgically. One (*Case 7*) was treated with x-ray alone. Another (*Case 9*) has been treated with radio active iodine (10). All, at one time or another, had undergone treatment with iodine.

Pathological reports of the thyroid gland were available in eight of the nine cases treated surgically.

Concurrent diseases known to be hereditary in nature and present in this family were studied. Of the 143 members in the family, 13 cases of arthritis were found (degenerative and rheumatoid). Six cases of tuberculosis, and five cases of rheumatic fever were discovered. Migraine headaches were present in four members of the family.

The incidences of miscarriages and stillbirths were of no statistical significance.

Of the 65 individuals who married into the family, only two findings relevant to thyroid disease were noted. These were cases of simple nontoxic goitre in two women, but these had no influence on the present study, as neither bore any children.

COMMENT

The mechanism of heredity in exophthalmic goitre is not clear. Ginsberg (28) felt that in the inherited forms of exophthalmic goitre the disease was confined almost exclusively to females and transmitted as a Mendelian dominant. Riebold (54) felt that it was the predisposition that was inherited as Mendelian dominants and recessives and that it was female sex-linked in a ratio of 3:1. Lenz (36) believed in dominant sex-linked genetic determinants in exophthalmic goitre. He explained that it was the "diathesis," not the disease that was transmitted, thus explaining incomplete syndromes or "formes frustes." Arullani (2), Brunet (7), Cockayne (14), Corning (15), Marine (36), and Souques (62) all believed that it was the predisposition to the disease that was inherited. Mangelsdorf (38) sum-

marizes it by saying that exophthalmic goitre, along with many other endocrine diseases, is probably transmitted on a Mendelian basis, but is greatly influenced by the many extrinsic and intrinsic factors that play on the individual and his endocrine system.

Of the reports in the literature, there are none which present enough cases or sufficient data to warrant conclusions which are statistically significant in regard to the mechanism of heredity in exophthalmic goitre. We attempted to analyze these reports as a whole, but due to the many individual inaccuracies and ommissions, such an approach was futile. Even with our relatively large number of cases, undisputed conclusions cannot be reached.

There is no question that exophthalmic goitre is more frequently seen in females, whether in its isolated or hereditary forms.

As far as could be determined, environmental factors were of no significance in the causation of exophthalmic goitre in this family. It had a heterogeneous geographical and occupational background and adhered to no dietary codes. Charcot (11), Dana (19), Moebius (42), and later Crotti (16), to cite but a few, believed that the hereditary form of exophthalmic goitre is strongly dependent on psychic factors in the family. These, of course, are very difficult to evaluate. The members with exophthalmic goitre in this family were first and second generation immigrants from Hungary and undoubtedly had many social hardships and anxieties, however, exophthalmic goitre has never been shown to have a higher incidence in immigrants.

Since the writing of this paper we have obtained family histories from several patients with exophthalmic goitre and almost invariably learned that one or two near relatives had been afflicted with the disease.

With only single cases of a thyroid adenoma (*Case 15*), hypothyroidism (*Case 16*), Addison's disease (*Case 7*) and diabetes mellitus (*Case 14*) in the family, we were unable to draw any correlations with the cases of exophthalmic goitre. Many papers have been written on familial and hereditary "dysthyroidism," that is, the presence of several types of thyroid disease and other endocrinopathies in one family; however, it is beyond the scope of this paper to discuss it and we have nothing conclusive to contribute.

CONCLUSIONS

Exophthalmic goitre is an inheritable disease but evidence is too meagre to warrant any conclusions in regard to the mechanism of heredity.

In the family we present, the incidence of other hereditary diseases was no greater than that seen in the general population.

The family incidence of exophthalmic goitre is probably greater than generally assumed.

SUMMARY

A family with 143 blood relatives in five generations, eleven of whom had exophthalmic goitre, has been studied. In addition, one member had a non-toxic thyroid adenoma and another had hypothyroidism.

Of the eleven persons with exophthalmic goitre, eight were females and three were males.

The disease made its appearance at ages varying from 26 to 61 years with no central tendency.

In all eleven cases there was convincing evidence of exophthlamic goitre, and case histories are herein submitted.

One patient with exophthalmic goitre developed Addison's disease and another developed diabetes mellitus.

A study was also made of other diseases known to be hereditary and occurring in this family; these included arthritis, tuberculosis, rheumatic fever, migraine headaches and diabetes mellitus.

We wish to express our thanks to Dr. James H. Means, Dr. R. W. Rawson, and Dr. Oliver Cope for their thoughtful suggestions and criticisms in preparing this paper. We would also like to thank the hospitals and physicians whose records we examined and without whose cooperation this paper could not have been written.

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LETTER

TO THE EDITOR:

The first Medical School in America was established in Mexico City in 1580. The student had the choice of studying Hippocrates in Greek or Hippocrates in Latin. No attention was paid to aboriginal American drugs: quinine, cocaine and nicotine. There are many who claim that action of these drugs was discovered in Europe. Recently Isidor Greenwald[1] claimed that goiter was brought to America by Europeans, and traveling by the silk route did not reach even England until 1717.

Where the American Indians left no records, it is difficult to determine whether they had goiter, but some later observations may be used in considering the probability. About 55 years ago I lived with primitive Mexican Indians. They called goiter "queschpoxahuatl." Other Central American Indians called it "huehuecho" (güegüecho). These American Indian names are very different from the Spanish name "bocio" for goiter. Usually the American Indians called what they got from the Spaniards by Spanish names.

The reverse relation in native names is shown in the Far East. Seaweed-eating Japanese have no goiter. I had to travel in Japan all day into a deep mountain valley (where the people lived largely on millet and got seaweed only in the wedding ceremony and of other seafood three dried minnows twice a week) to find a goiter. In Japanese Medical Schools goiter is called "kōzyōsensyu" which is a Japanese name for four Chinese words with which Chinese describe goiter. Although Wang and Wu state that the Chinese used the thyroid gland in medicine in 627, the Chinese have no idiogram (Chinese character) for goiter. Perhaps their ideogram-inventiveness gave out before they recognized goiter as of sufficient importance to be recorded. If goiter was spread by the silk industry (as claimed by Greenwald) which had its origin in China, one might suppose goiter originated in China. The lack of an ideogram for goiter might indicate that it was not as prevalent in ancient times even in China as it is today.

Before Kocher perfected thyroidectomy many goiters were called "bronchocele" which means a tumor of the windpipe and was supposed to be filled with mucus. This error was corrected by inspection made possible by surgery, and the word "aerocele" coined for the original meaning. This ancient error was re-enacted in 1938 in a large hospital; *i.e.* mistaking a goiter for a tumor of the windpipe. Before the study of the histology of the thyroid gland it was natural to confuse large accumulations of thyroid-col-

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[1] Greenwald, I. Early history of goiter in the Americas, in New Zealand, and in England; contribution to the etiology of disease. *Bull. Hist. Med. 17:* 229–268 (1945).

loid with contents of an aerocele or bronchiectasis. Failure to diagnose goiter is widespread today. Many newborns are classified as cases of "congenital weakness" whereas the true diagnosis is goiter. In a city school of supposedly normal pupils a public health agency found that 96 per cent of the girls had goiter.

Since pre-Columbian American Indian surgery was largely confined to trephining the skull under cocaine anesthesia, one would not expect them to relate goiter to the thyroid gland. Although Roger de Palermo prescribed burnt sponge and ash of seaweed for goiter in 1180 it was not considered a disease by the general public, but on the contrary was considered a mark of feminine beauty by the old masters.

To sum up, the attempt to trace the history of goiter is hampered by failure of ancient peoples to recognize it as a disease, uncertainty of names due to uncertainty of diagnosis and lack of recorded literature. Many details about the American Indians were never mentioned, probably not even observed by the early explorers. Greenwald remarks on the "perfect health" of the American Indians. But what is health? Simple goiter is not admitted to many hospitals in the U. S. A. and Canada because "the beds are reserved for sick people."

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Announcements

TWENTY-FIFTH ANNIVERSARY OF THE DISCOVERY OF INSULIN

The twenty-fifth anniversary of the discovery of Insulin will be observed with a program in Convocation Hall, at the University of Toronto, on September 16. Many internationally known figures in the field of medicine will be present to honor the occasion. Among them will be R. D. Lawrence, physician in charge, Diabetic Clinic, Kings College Hospital, London, England; H. C. Hagedorn, of Gentofte, Denmark; Bernardo A. Houssay, Research Institute of Experimental Biology and Medicine, Buenos Aires, Argentina; and Elliott P. Joslin, Harvard Medical School, Boston, U.S.A. This observation will be followed by the regular annual meeting of the American Diabetes Association.

On September 23 Eli Lilly and Company will sponsor an International diabetes clinic to be held at the Indiana University Medical Center in Herty Hall of the State Board of Health Building, Indianapolis, Indiana. Professor Charles H. Best, Toronto, Canada, co-discoverer with Banting of Insulin, Professor Houssay, Dr. Lawrence, and Dr. Hagedorn will discuss various phases of the subject of diabetes.

TENTATIVE PROGRAM
INTERNATIONAL DIABETES CLINIC

Herty Hall, of the Indiana State Board of Health Building,
Indiana University Medical Center, Indianapolis, Indiana,
September 23, 1946

2:00 P.M.—Ten-minute addresses

1. Dr. J. O. Ritchey, Professor of Medicine, Indiana University School of Medicine: Address of Welcome
2. Dr. Franklin B. Peck, Lilly Research Laboratories
   Introductions: Dr. Moses Barron, Minneapolis
   Dr. W. D. Sansum, Santa Barbara
   Dr. G. H. A. Clowes, Research Director Emeritus, Lilly Research Laboratories
3. Dr. Joseph H. Barach, Falk Clinic, Pittsburgh, Retiring President of A.D.A.: "Twenty-Five Years of Insulin"
4. Professor Charles H. Best, Toronto, Canada: "The Discovery of Insulin"
5. Dr. John R. Williams, University of Rochester: "Sir Frederick Banting"
6. Professor Bernardo A. Houssay, Buenos Aires: "Etiology of Diabetes"
7. Dr. R. D. Lawrence, King's College Hospital, London: "Diabetes in England"
8. Professor Carl Cori, Washington University, St. Louis: "The Action of Insulin"
9. Dr. H. C. Hagedorn, Gentofte, Denmark: "Modification of Insulin"
10. Dr. Elliott J. Joslin, Boston: "Problems of the Future"

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor; D. A. McGINTY. *Collaborators:* A. R. ABARBANEL, F. N. ANDREWS, B. L. BAKER F. A. DE LA BALZE, ISRAEL BRAM, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS ANNA FORBES, M. B. GORDON, H. S. GUTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MCARTHUR, THOMAS H. MCGAVACK A. E. MEYER, K. E. PASCHKIS, A. B. PINTO, J. R. REFORZOMEMBRIVES, E. C. REIFENSTEIN JR., G. G. RUDOLPH, L. T. SAMUELS.

GONADS

CHU, J. T., B. C. LEE AND S. S. YOU. Functional relations between the uterus and the corpus luteum *J. Endocrinol. 4:* 392 (1946).

Survival of corpora lutea in pseudopregnant rabbits was prolonged by hysterectomy, restored to normal by implantation of uterine tissue. If estrone injections were made into either the normal pseudopregnant animals or those with implants, the function of the luteal tissue was maintained. Removal of the uterus from pregnant rabbits speeded regression of the corpus luteum. Implantation of the placenta or injection of estrone into hysterectomized pregnant animals prolonged the survival of the corpus luteum. The authors draw the inference that estrogen is essential for the maintenance of luteal function and that the placenta supplies this in the pregnant animal while the uterus destroys it in the pseudopregnant animal.—*L.T.S.*

CULINER A. The relation of the theca cells to disturbances of the menstrual cycle. *J. Obst. and Gynaec. Brit. Emp. 52* (6): 545 (1945).

The question of estrogen production by the theca cells and luteinization of this tissue was discussed. It was pointed out that a correlation existed in the baboon between extensive theca-luteinization and irregularity of the menstrual cycle. The aim of the present study was to investigate the relation of alteration in the theca cells of the human ovary into yellow plaques in individuals with an abnormal menstrual rhythm. Ovaries and uteri of women operated on because of bleeding or other evidence of endocrine disorder were studied. The ovaries were studied histologically. Illustrations included 11 micrographs. It was concluded that theca cell proliferation may occur as part of the maturation process of the Graafian follicle, that theca cell luteinization in atretic follicles is a part of the normal atretic process of no clinical significance, that luteinized theca cells exert an endocrine influence, the nature of which is not definitely known. The character of the uterine reaction found with theca cells implied activity of some hormone having an androgenic rather than estrogenic or progestational effect.—*R.A.C.*

GARTSIDE, I. B. Occurrence of ovulation and causes of sterility in metropathia haemorrhagica, *Brit. M. J., 1:* 604 (1946).

A case is reported of a patient aged forty with a history of prolonged bleeding with

cycles varying from 28 to 35 days. On subtotal hysterectomy a cystic right ovary was found, the left ovary being normal. The uterus showed a mixed secretory and proliferative endometrium with a polyp-like structure which consisted of degenerate chorionic villi. The conclusion is reached that ovulation occurs in such cases but that sterility is due to the inability of the ovum to imbed itself in an endometrium which is incompletely prepared for its reception.—*L.T.S.*

PANCREAS

GENDEL, B. R. AND J. E. BENJAMIN. Psychogenic factors in the etiology of diabetes, *New England J. Med. 234:* 556 (1946).

In an attempt to determine the role of psychogenic factors the authors made a careful study of the history of 44 cases of diabetes observed in 21,993 admissions at Lovell General Hospital. While a number of the cases gave a history of onset after emotional stress in combat they did not conform to Menninger's criteria of psychogenically induced diabetes, since they showed no improvement of the mental state which could not be accounted for purely on the basis of improved dietary control. The authors also think that the incidence of diabetes in the army is no greater than in civilian life. They, therefore, are inclined to doubt the role of psychogenic factors in the development of permanent diabetes.—*L.T.S.*

GERBER, P. Estrogenic therapy in diabetes. *Pennsylvania M. J. 49* (7): 744–747 (1946).

This is a good review of the subject. Ten cases of diabetes mellitus were treated with estrogens and/or stilbestrol for a period of three months, with an average reduction of 31.6 per cent in their total daily insulin requirements, and a general improvement in their sense of well-being. Reference is made to the conflicting reports in the literature concerning the results of estrogen therapy in the female diabetic, and a theory is offered to explain these differences. Experimental and clinical studies are quoted to stress the value of early institution of therapy in the newly discovered diabetic, with an eye toward increasing the incidence of remissions in diabetes. Two large groups selected by the author to receive estrogen therapy would be menopausal diabetics and diabetics of any age group who demonstrated signs of hyperpituitarism, hypoovarianism, or both.—*I.B.*

HULBERT, N. G. AND R. J. MCN. LOVE. Spontaneous hypoglycemia associated with epilepsy; subtotal pancreatectomy, *Brit. M. J. 1:* 603 (1946).

A case is reported in which attacks of spontaneous hypoglycemia followed a history of epilepsy. The patient died after operation for subtotal pancreatectomy. Careful examination of the pancreas revealed no adenoma and no evidence of hyperplasia of the islet tissue. The only abnormality found on extensive autopsy was in the brain. Since careful search revealed no excess islet tissue the hypothesis is advanced that the hypoglycemia is the result of a lesion of the hypothalamus.—*L.T.S.*

JOHN, H. J. Does the fractional daily urine examination on a diabetic patient furnish us the ideal means of control? *South. M. J. 23:* 60–63 (1946).

The advisability of fractional daily urine examination in diabetic patients was discussed and the usual laborious procedures were deplored and their importance ques-

tioned. Factors to be considered in estimating the significance of glycosuria are the renal threshold for sugar and the actual amount of sugar excreted per 24 hours. Since the renal threshold for sugar is not a fixed factor and urinary excretion is variable, three blood sugars per day (taken before meals) were advocated when glycosuria is observed. The adjustment of insulin doses is to be made on basis of these blood studies. In addition the author advised the determination of actual excretion of sugar per 24 hours and if the total amount exceeded 10 grams, increase in insulin dosage is indicated. Intermittent glycosuria does not require adjustment of insulin administration providing the total sugar excretion is less than 10 grams per 24 hours.—*H.S.K.*

JOSLIN, E. P. Medical progress: Diabetes mellitus, *New England J. Med., 234:* 442–448 (1946).

The article is a review of certain fields of diabetes mellitus. The discussion of the effects of alloxan covers most of the recent literature. There is also a good general discussion of diabetic neuropathy. The discussion of diabetes in children is largely devoted to a paper by Lichtenstein of Stockholm. A paper on statistics of diabetes in Finland is also included. The article ends with a comprehensive review of all the various organizations interested in diabetes.—*L.T.S.*

MELVIN, J. P., JR. AND H. T. ENGLEHARDT. Observations on the treatment of diabetes mellitus complicated by pulmonary tuberculosis. *South M. J. 39:* 64–67 (1946).

Roentgenological examination of 53 cases of diabetes mellitus revealed 4 patients showing definite x-ray evidence of pulmonary tuberculosis, while 4 had strongly suggestive and 3 had slightly suggestive x-rays. Tuberculosis in diabetics showed certain peculiarities. Nearly 50 per cent of all patients showed evidence of cavitation. Pleural adhesions were more common in diabetics yet tuberculosis involvement of the other serous structures other than the pleura was very rare. The relationship of coma to pulmonary tuberculosis is significant since 75 per cent of the patients in the present series who had had coma developed pulmonary tuberculosis. The prognosis of the patient with tuberculosis and diabetes is the same as that of the acid fast infection itself. Treatment of the combined disease entities should include the usual principles employed in the treatment of tuberculosis. The diet should be so regulated that the patient would be permitted to attain his optimal weight. A moderate hyperglycemia may be permitted and the patient is to be considered as regulated if he spills 5 per cent or less of the total ingested carbohydrate in 24 hours and providing there is no acetonuria. Tubercular diabetics must be well controlled and usually require doses of protamine zinc and unmodified insulin on the sliding scale. In view of the high incidence of tuberculosis complicating diabetic coma all cases of coma should have careful and repeated roentgenological examination.—*H.S.K.*

RUDY, A. Diabetic neuropathy. *New England J. Med. 233:* 684–689 (1945).

The problem of neurologic abnormalities accompanying diabetes is discussed and eight cases are presented. The mere control of glycosuria with or without insulin does not prevent the development of this neuropaphy. Since the symptoms resemble those of thiamin and riboflavin deficiency these vitamins were used in the treatment of this condition with success in the cases reported. The rate of recovery, however, varied widely, some cases demanding intensive and prolonged therapy.—*L.T.S.*